GARDASIL® in the Prevention of Anal Cancer

Vaccines and Related Biological Products
Advisory Committee Meeting
November 17, 2010

Merck Research Laboratories

Agenda

- Joel Palefsky, MD
  - Anal HPV infection, AIN and anal cancer
- Patrick Brill-Edwards, MD
  - Current status of GARDASIL®
  - Proposed indication
- Elizabeth Garner, MD, MPH
  - The role of HPV in anal cancer in men and women
  - The burden of anal cancer in men and women
  - High-grade anal intraepithelial neoplasia (AIN 2/3): the precursor of anal cancer
  - AIN study design and results
  - Postlicensure surveillance and longer term studies
  - Rationale for an anal cancer indication in males and females

Anal Cancer

- Anal cancer is an HPV related cancer
- The incidence of anal cancer has been increasing at ~2% per year for the last three decades
- Men who have sex with men (MSM) are at particularly high risk for anal HPV-associated disease
  - HPV-related anal disease has been most extensively studied in this population
  - MSM were evaluated in the efficacy study we will discuss later this morning
- Anal cancer is a disease of men and women
  - Women account for 60% of the cases of anal cancer

Joel Palefsky, MD, CM, FRCP(C)

- Professor of Medicine, University of California, San Francisco
- Board-certified in Internal Medicine (McGill University, Montreal, Canada)
- Board-certified in Infectious Diseases (Stanford University)
- Founder and Director, UCSF Anal Neoplasia Clinic
- Founder and Chair, NCI AIDS Malignancy Consortium HPV Working Group
- Member of the Board, American Society for Colposcopy and Cervical Pathology, International Papillomavirus Society
- Member of the Board, Foundation for HPV and Anal Cancer

Anal HPV infection, AIN and anal cancer

FDA meeting

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Disclosures

Merck and Co.

Recipient of grant funding

Member, Scientific Advisory Boards

Investigator on Merck 020 protocol

Pharmjet Inc.

Scientific Advisory Board

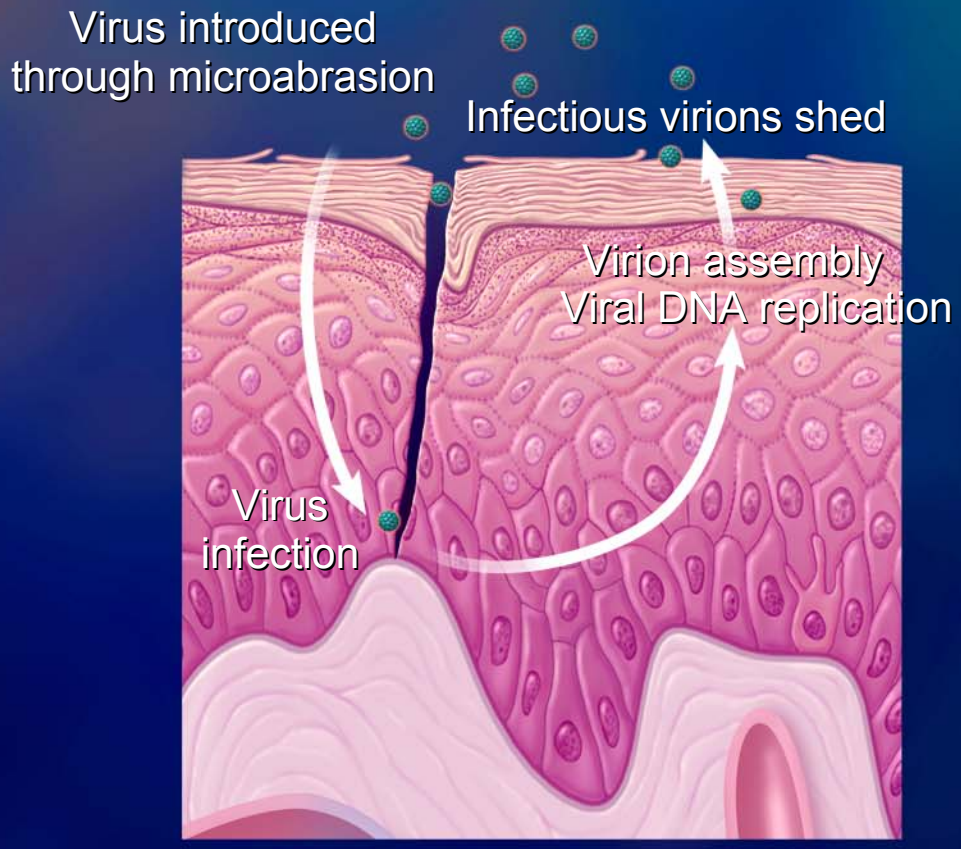
Aura Biosciences Inc.

Scientific Advisory Board

Outline

- Biological similarity between anal and cervical cancer
- Anal HPV infection
- Demographics and risk factors for anal cancer
- High-grade anal intraepithelial neoplasia (AIN) as precursor to anal cancer
- Screening and treatment of AIN
- Concluding remarks

HPV infection and productive life cycle



Late HPV protein production
L1 & L2

Early HPV protein production
E1, E2, E4, E5, E6, & E7

Adapted from Doorbar J. *J Clin Virol*. 2005;32S:S7–S15.

Biological similarity between anal cancer and cervical cancer

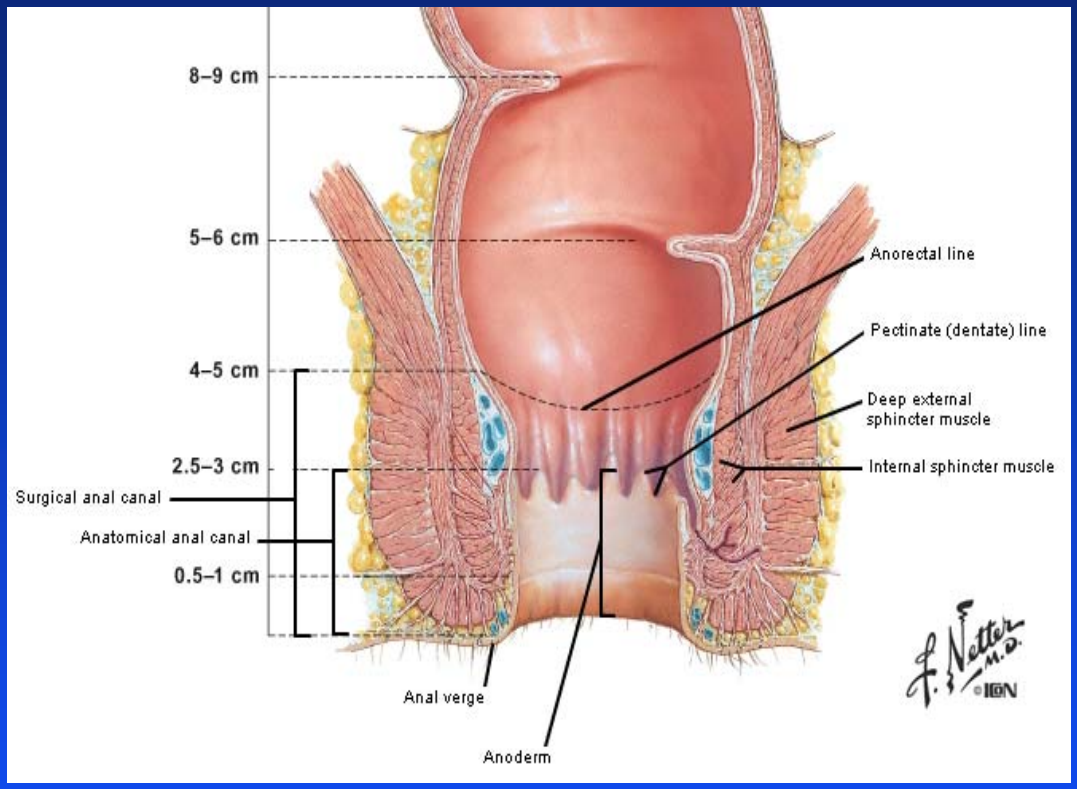
Anatomic similarity:
Transformation zones

Morphologic similarity:
Precursor lesions and cancer

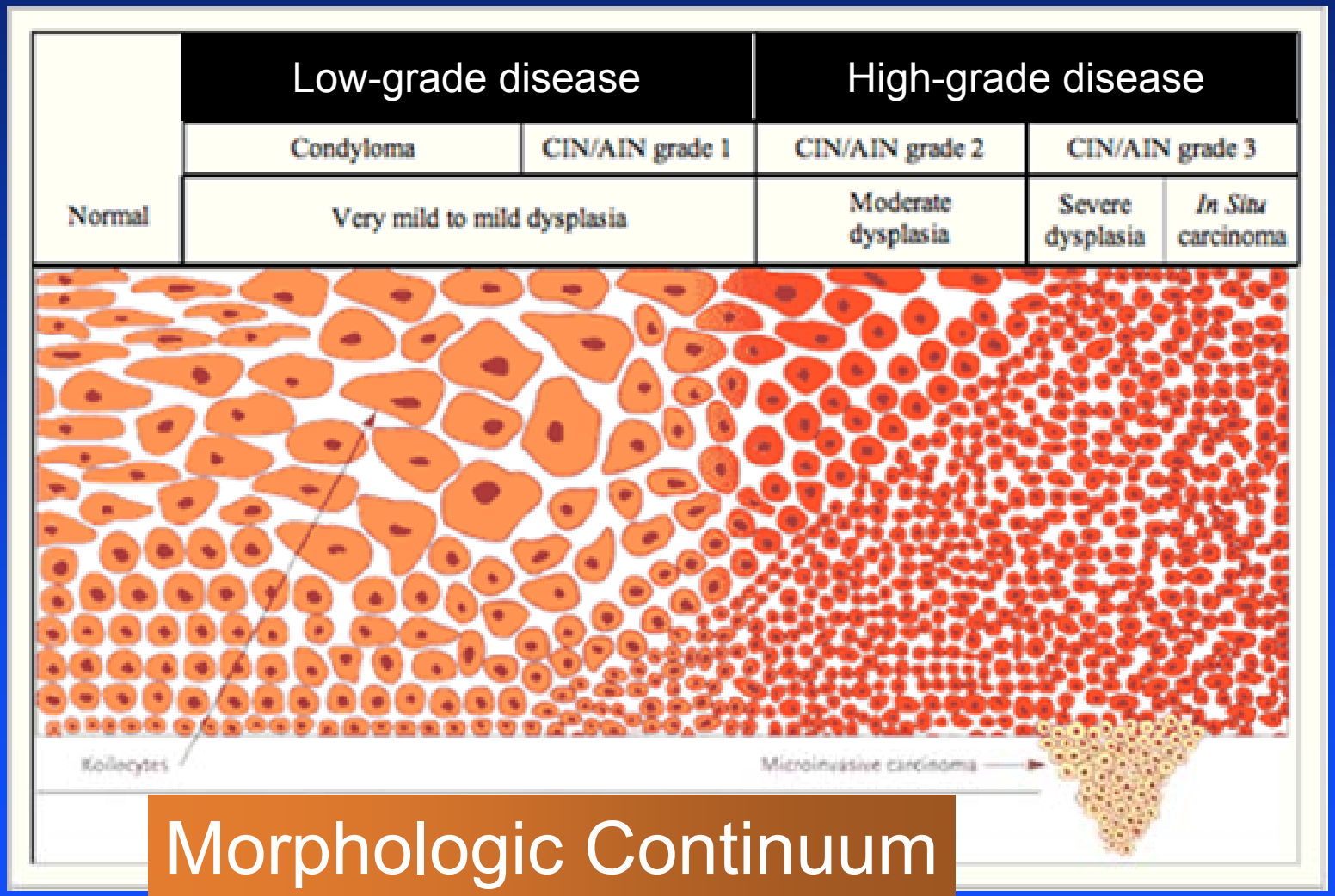
Etiologic similarity:
Association with HPV

Anal transformation zone

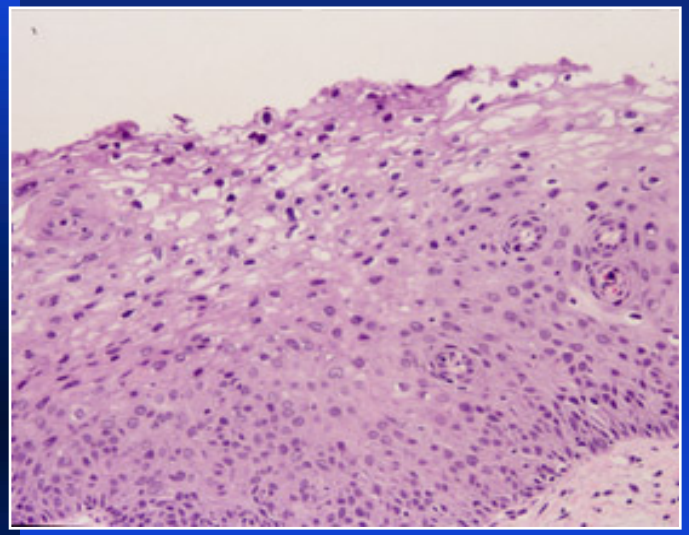
- Morphologically analogous to the cervical transformation zone
- Region of squamous metaplasia
- "Immature" squamous metaplasia
  - Leading edge at squamo-columnar junction
  - Most susceptible to oncogenic HPV



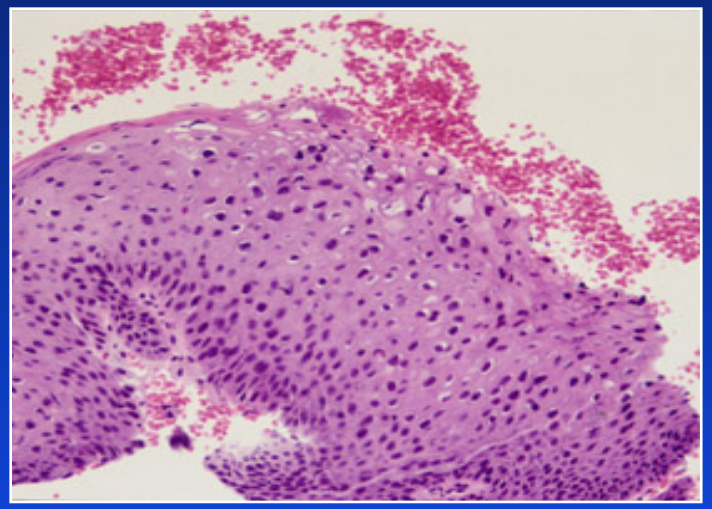
Spectrum of HPV disease

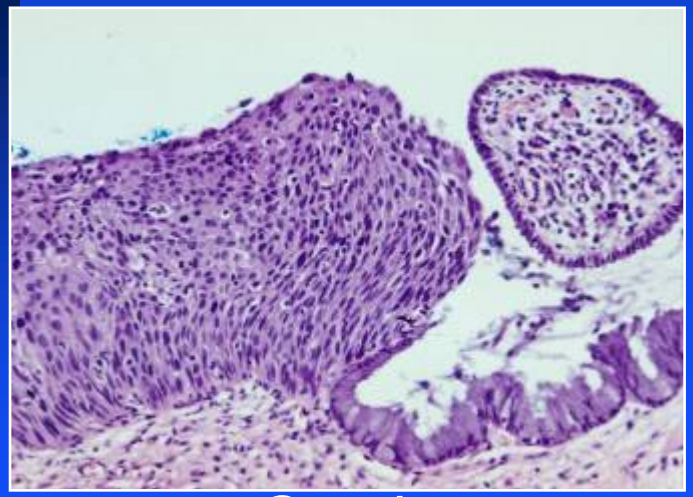


Cervix and anus: lesions morphologically similar

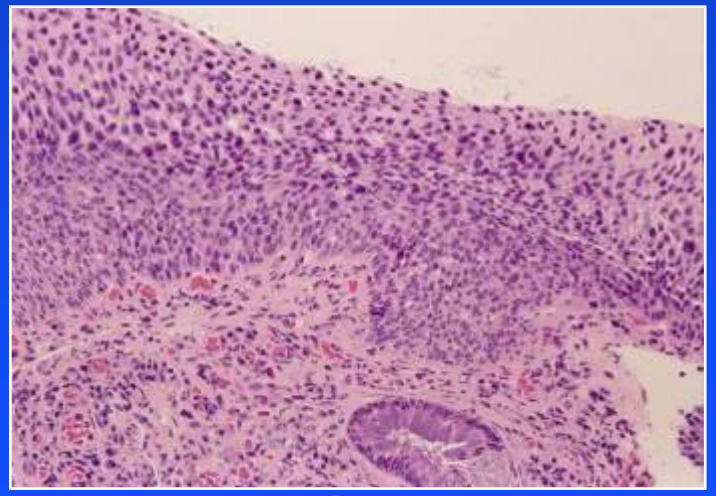


Low-grade





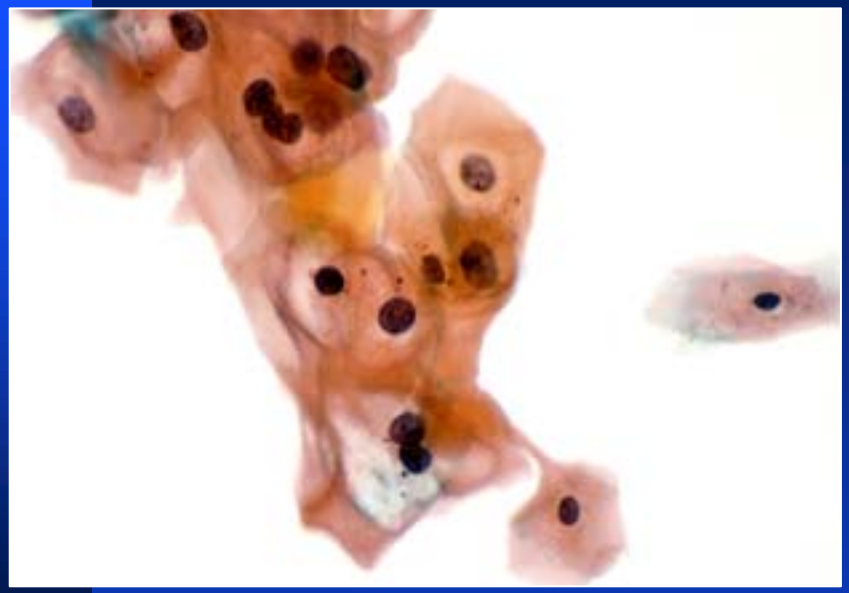
High-grade

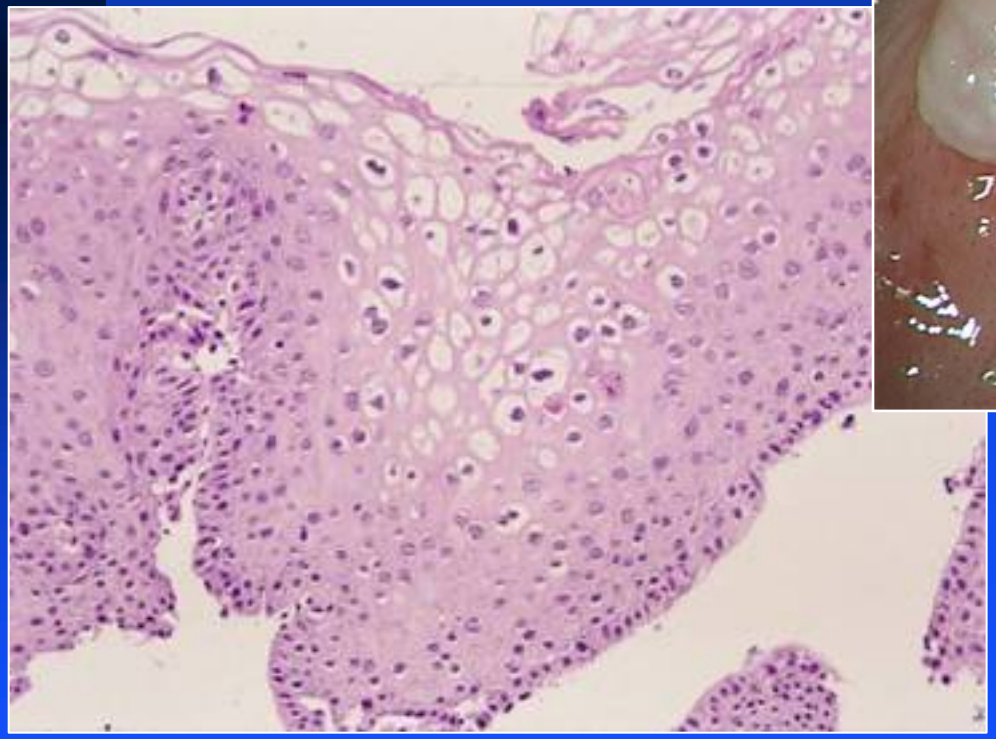


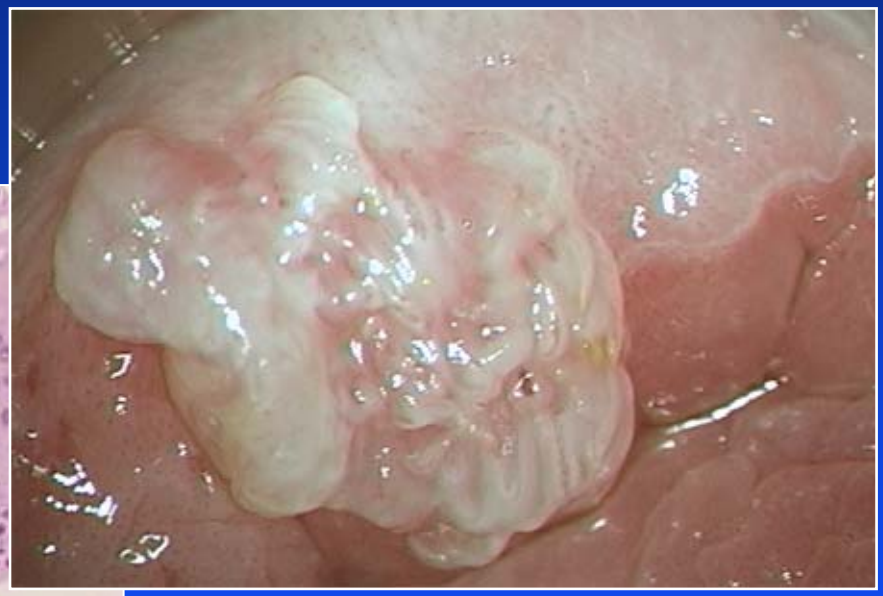
Cervix

Anus

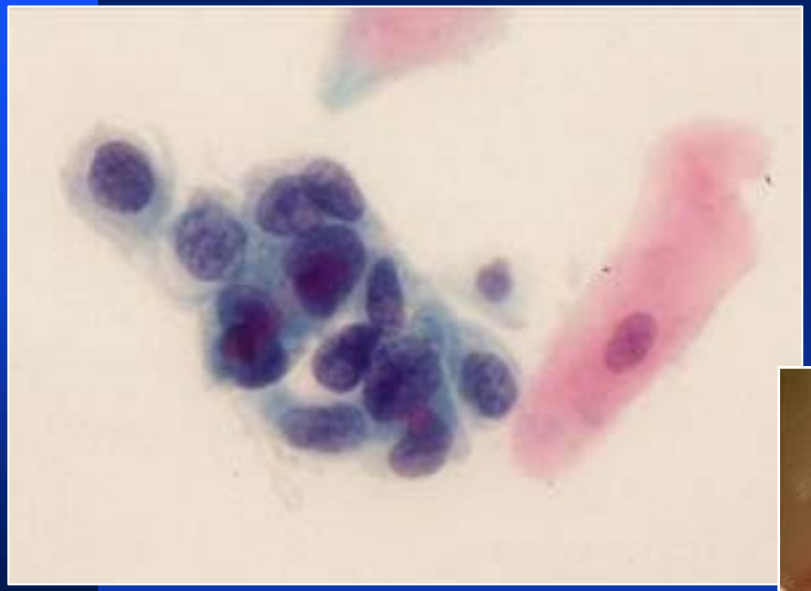
Low-grade

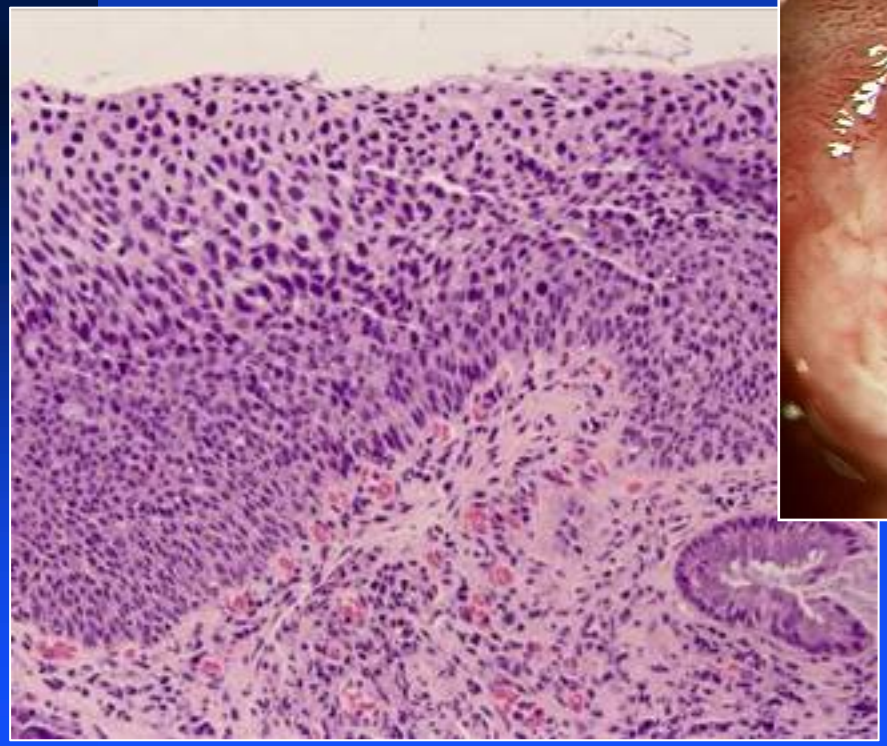


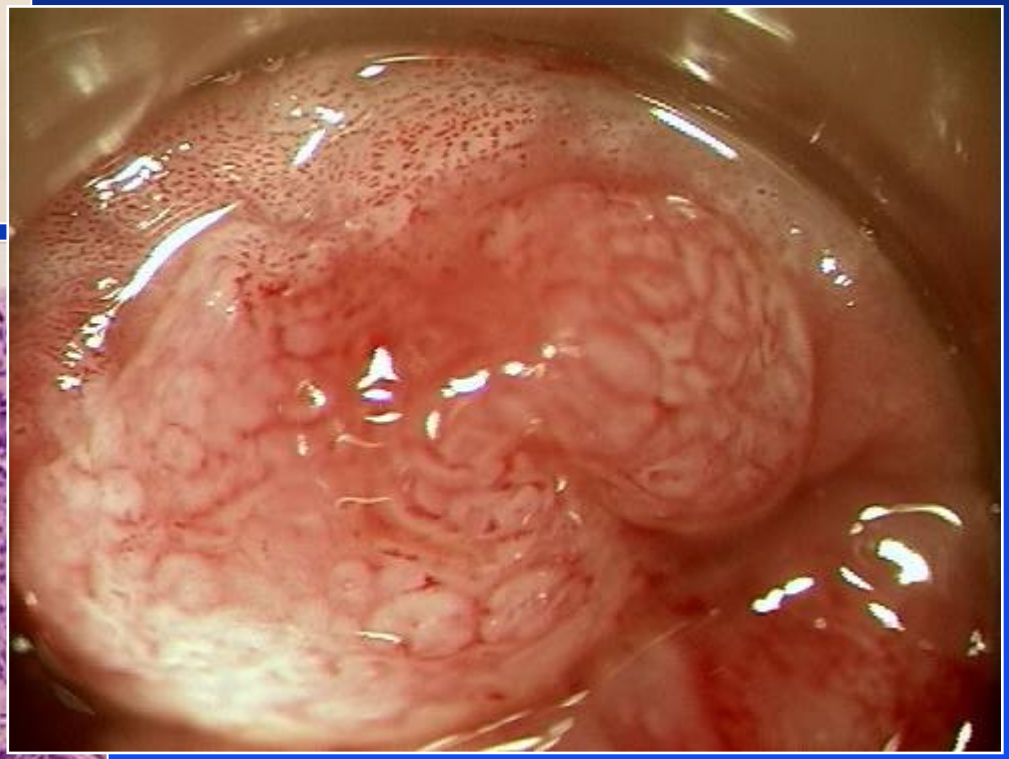




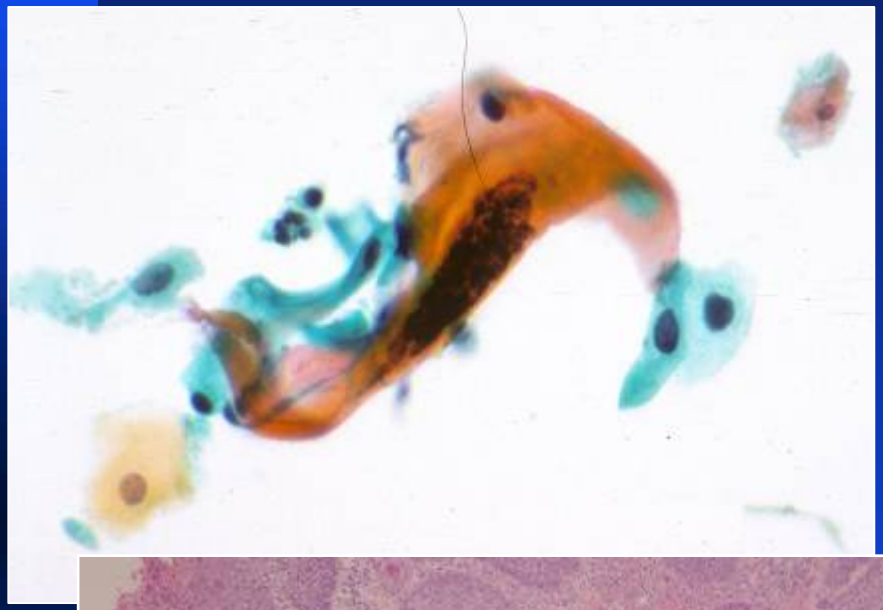
High-grade

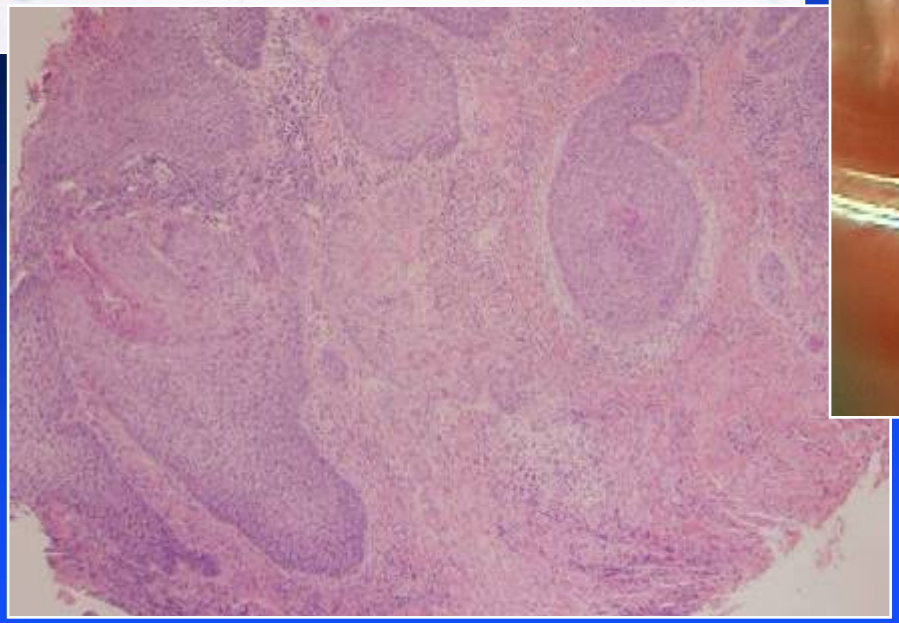


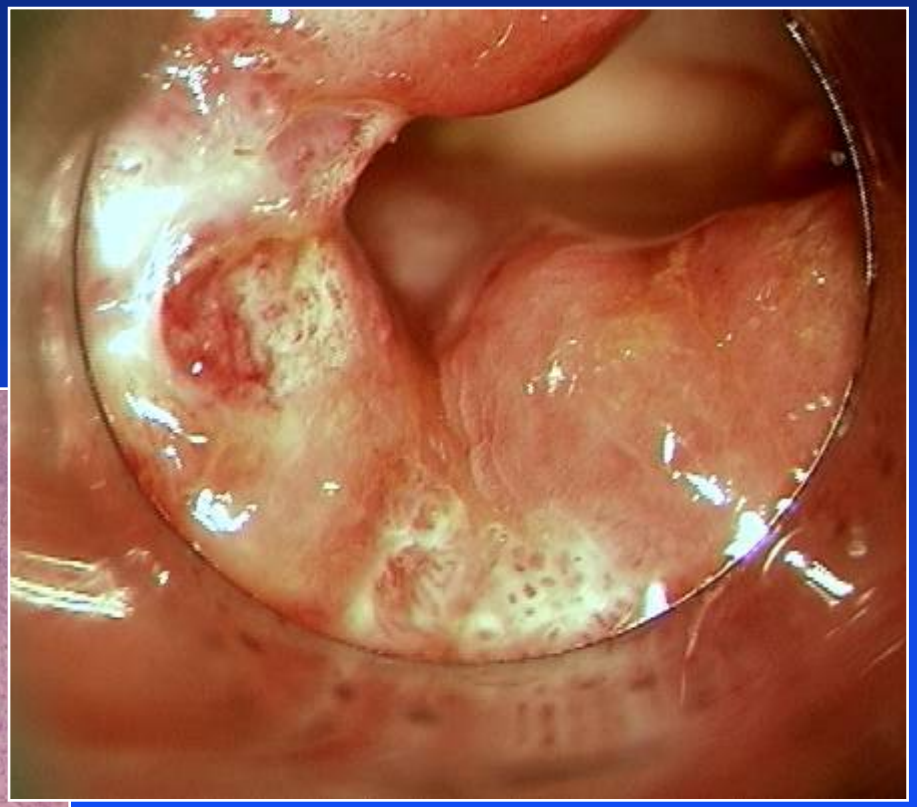




Anal cancer

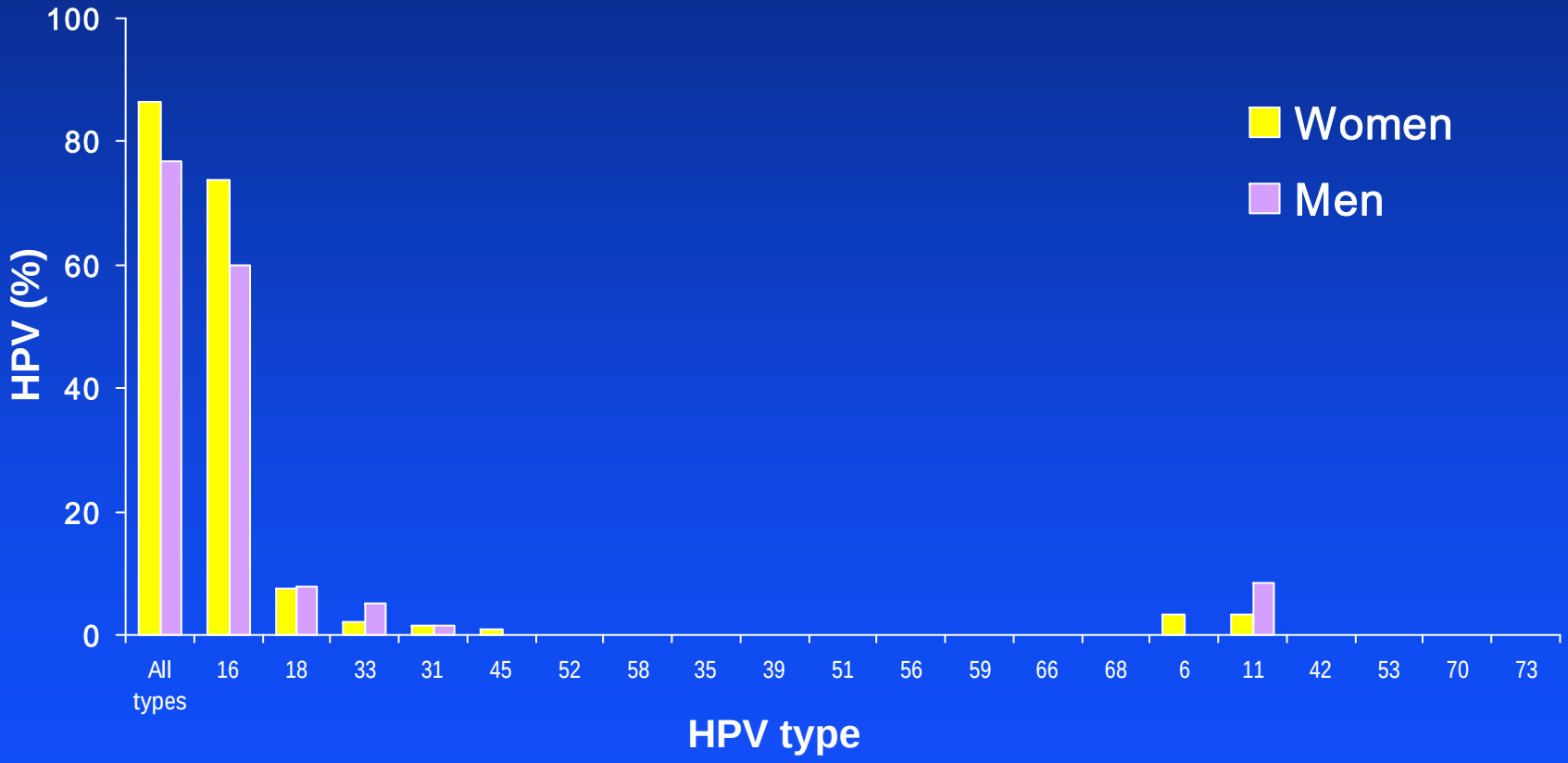






Anal cancer and cervical cancer have a similar etiology

Anal cancer is the same in men and women

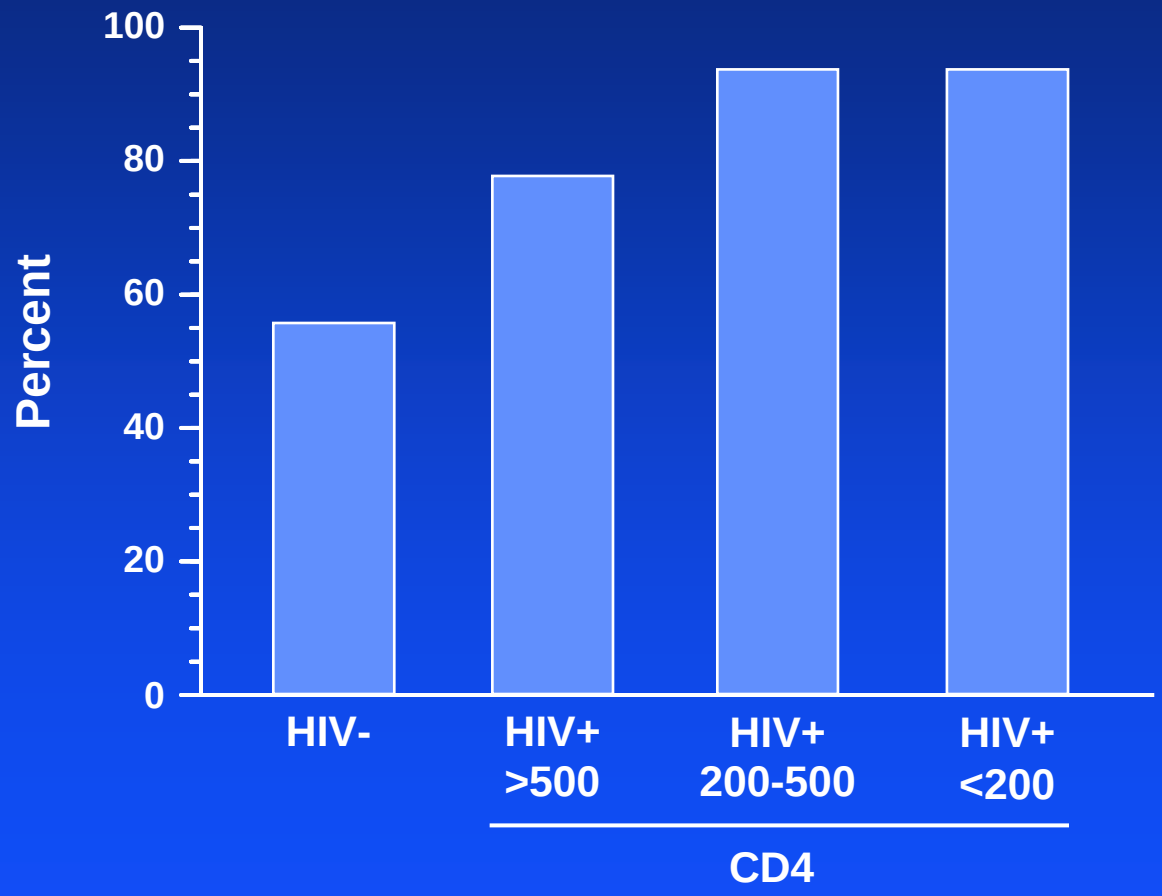


Hoots, BE et al. *Int J Cancer*. 2009;124:2375-2383

Anal cancer incidence

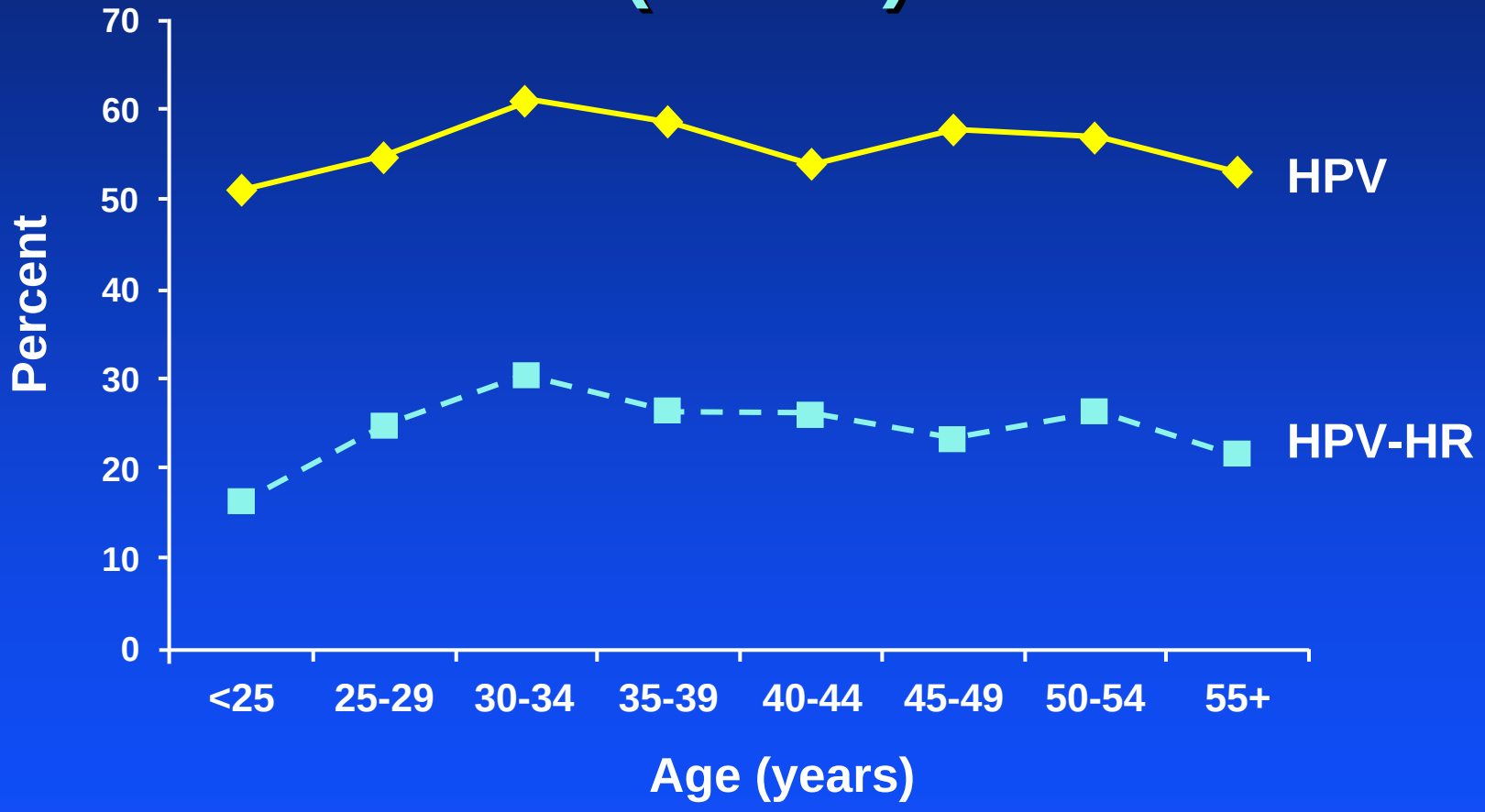
- Incidence highest in men who have sex with men
- Most anal HPV infection and AIN natural history data are from MSM
- Absolute numbers of cancers are higher in women and men who have sex with women

Percent of men who have sex with men (MSM) with anal HPV infection



Palefsky JM et al. *J Infect Dis.* 1998;177:361-367.

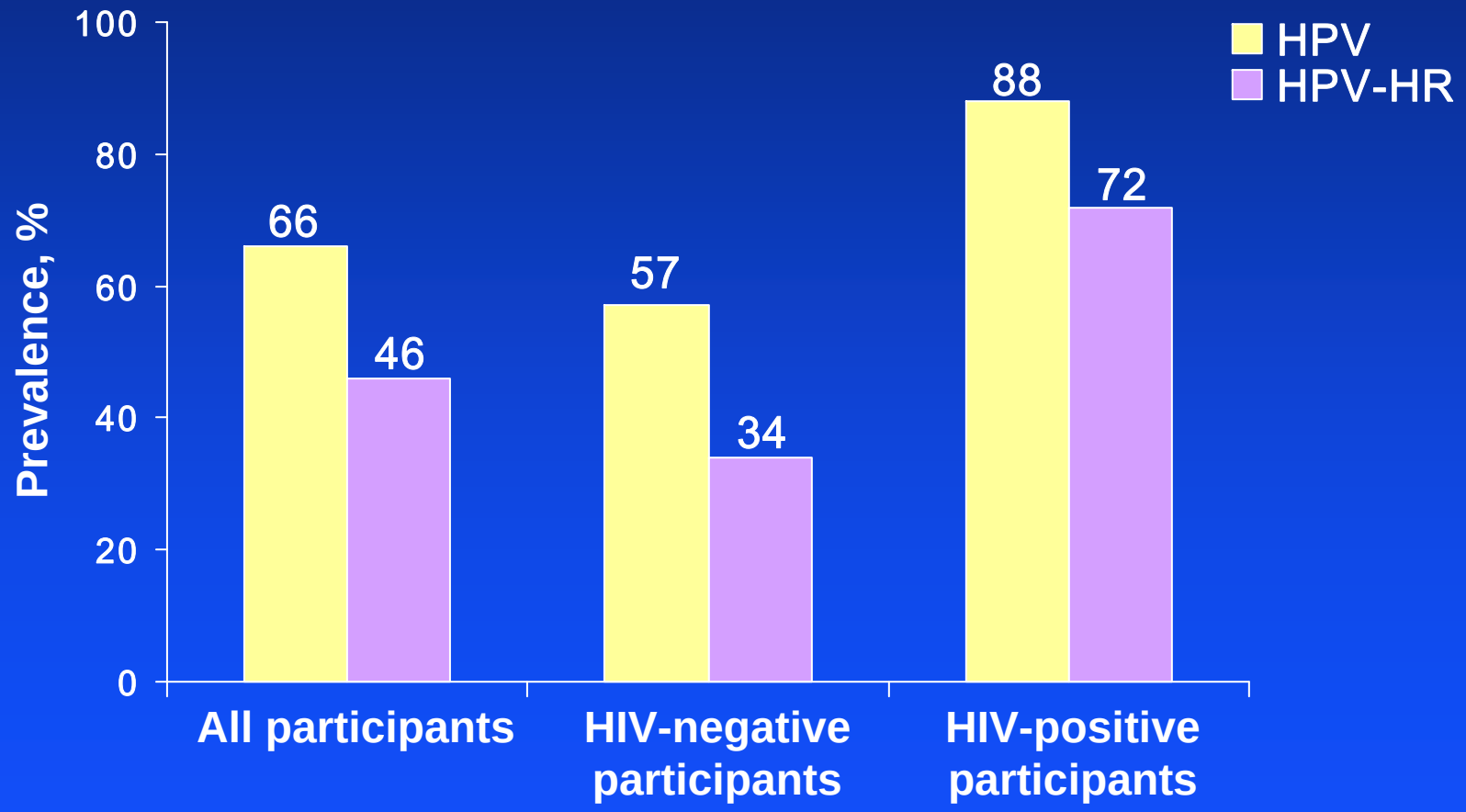
Anal HPV infection by age group in sexually active HIV-negative MSM (≈1400)



HPV-HR=HPV high-risk.

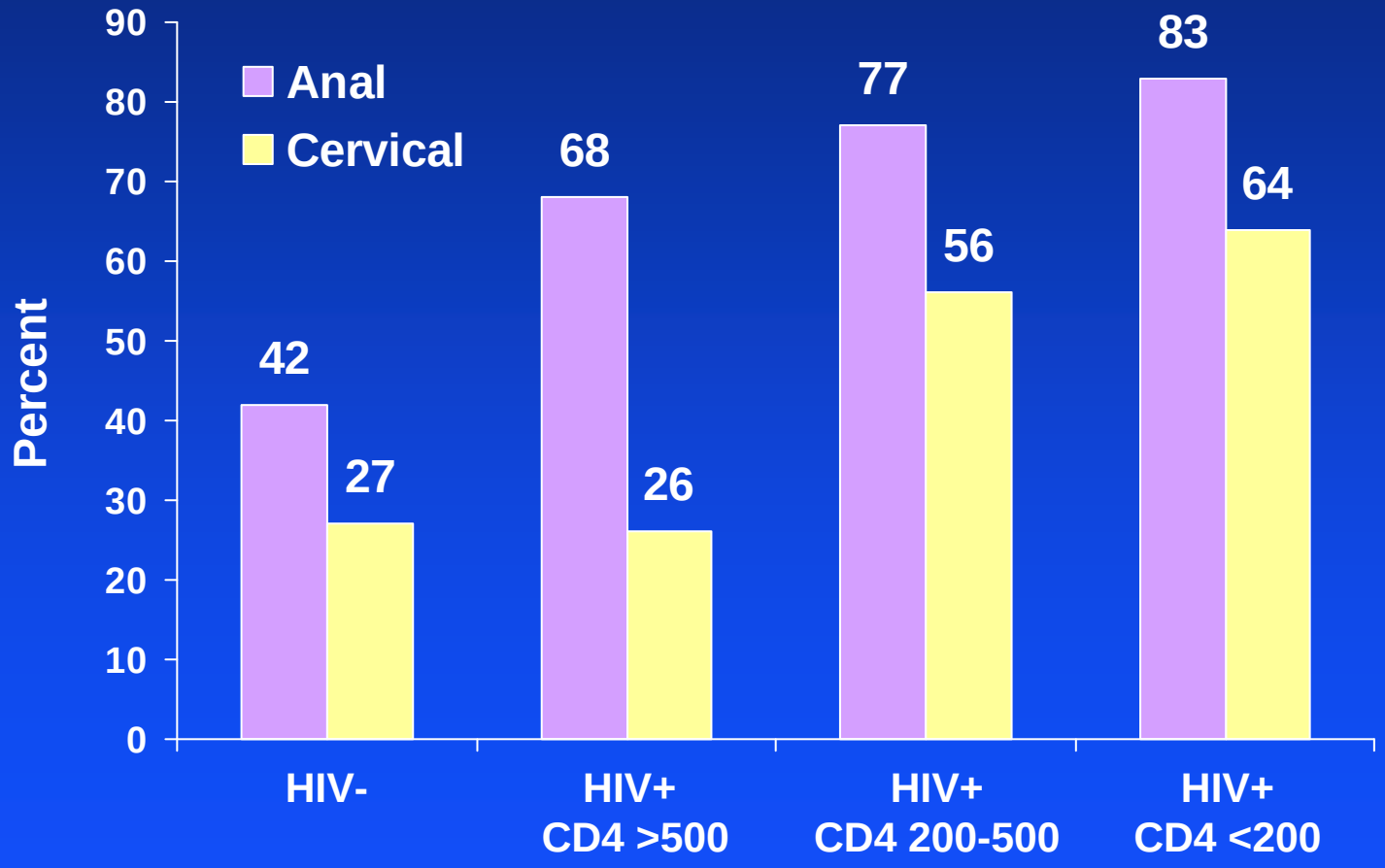
Chin-Hong PV et al. *J Infect Dis*. 2004;190:2070-2076.

Prevalence of anal HPV among MSM
Population-based data



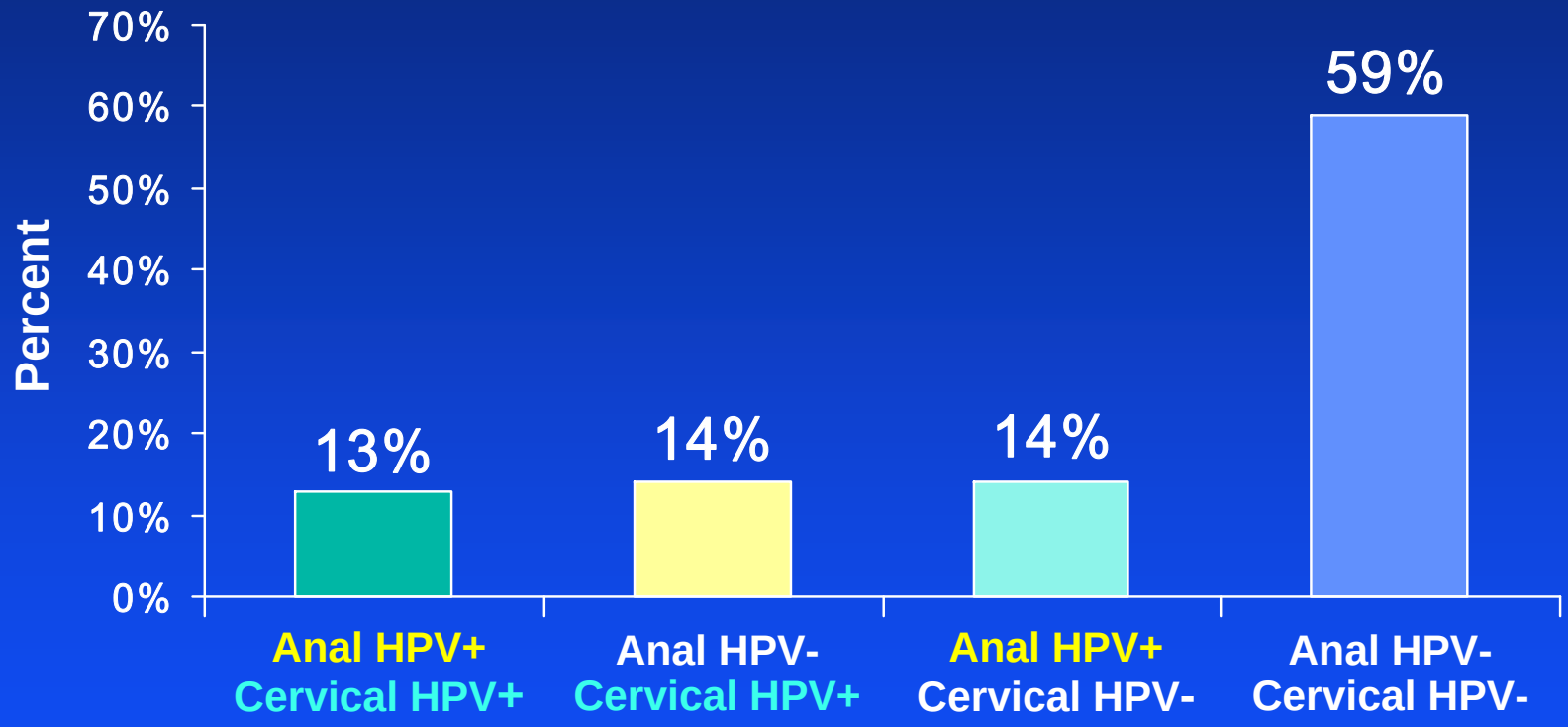
Chin-Hong et al. *Ann Int Med*. 2008;149;300-6.

Anal and cervical HPV infection in HIV-positive women and HIV-negative women at high risk of HIV infection



Palefsky JM et al. *J Infect Dis*. 2001;183:383-391.

Prevalence of cervical and anal HPV infection in healthy HIV-negative women



N=1566 healthy women who provided cervical and anal specimens.

Modified from Hernandez BY et al. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2550-2556.

Prevalence of anal HPV infection among Tampa men who have sex with women in the "HPV in Men Study"

Variable	No. (%) of men (n=278)
Any HPV type	36 (13.0)
Any oncogenic type	24 (8.6)
Types 6 or 11	6 (2.2)
Types 16 or 18	20 (7.2)

Nyitray, A et al. *J Infect Dis.* 2010; 201:1498–1508.

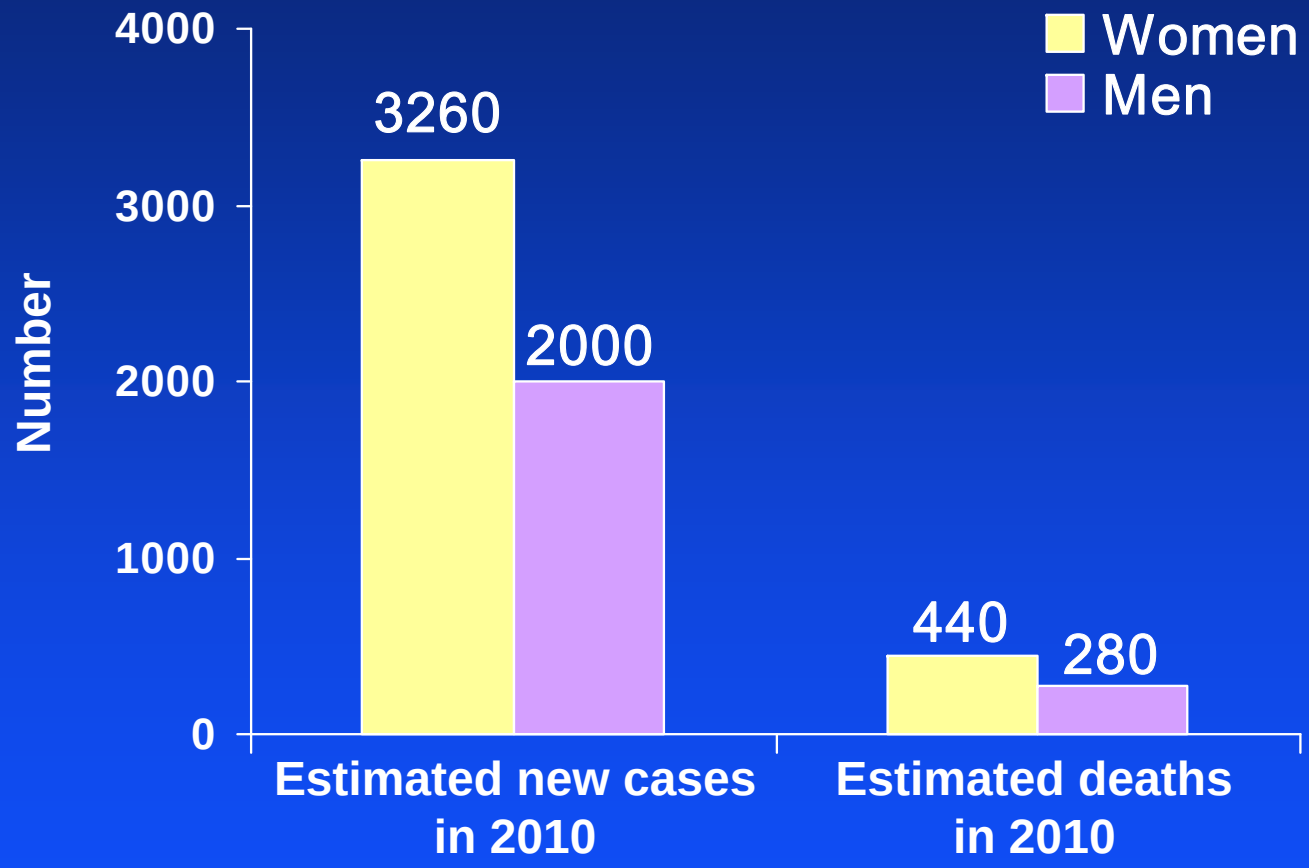
Risk factors for anal HPV infection

- Men and women
  - Receptive anal intercourse
  - Immune suppression
  - Fingers, toys?
- Men
  - Spread from perianus, penis, scrotum?
- Women
  - Spread from cervix, vulva?

Clinical implications of anal HPV infection

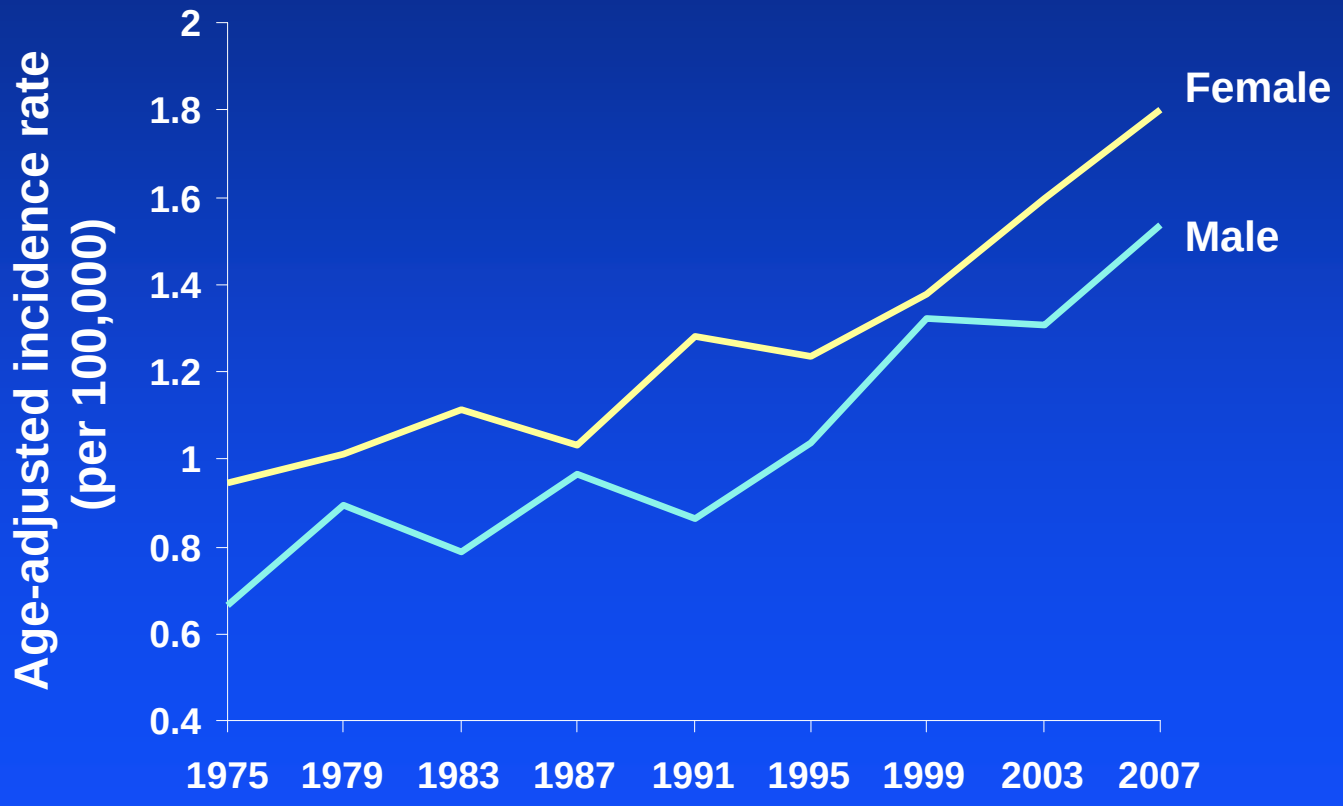
- Anal cancer
- Anal intraepithelial neoplasia 2/3
- Anal condyloma

Anal cancer in the U.S.



American Cancer Society: www.cancer.org

Age-adjusted incidence rate of anal cancer by gender and year of diagnosis



Anal and cervical cancer incidence

- Cervical cancer prior to cervical cytology screening: 40-50/100,000
- Cervical cancer currently: 8/100,000
- Anal cancer among HIV- MSM: up to 37/100,000

Relative risk of anal cancer in U.S. AIDS-cancer registry match study

Age (years)	HIV+ women	HIV+ men
30-39	12.2	40
>40	2.6	32
All ages	6.8	37.9

Frisch et al. *JNCI.* May, 2000.

Recent reports of incidence in anal cancer since introduction of HAART

- 75/100,000 person-years among HIV+ MSM since 1999
  - Piketty C, Selinger-Leneman H, Grabaret S, et al. *AIDS*. 2008;22:1203-1211
- 78/100,000 person-years among HIV+ MSM since 2000
  - Patel P, Hanson H, Sullivan S, et al. *Ann Intern Med*. 2008;10(148):728-736
- 137/100,000 person-years among HIV+ MSM since 1996
  - D'Souza G, Wiley D, Li X, et al. *J Acquir Immune Defic Syndr*. 2008;48(4):491-499.

Risk factors for anal cancer

- HPV is necessary but probably insufficient
- Number of sexual partners
- Receptive anal intercourse
- Current smoking
- History of fissures/fistulas/hemorrhoids
  - Anal cancer in MSM > women

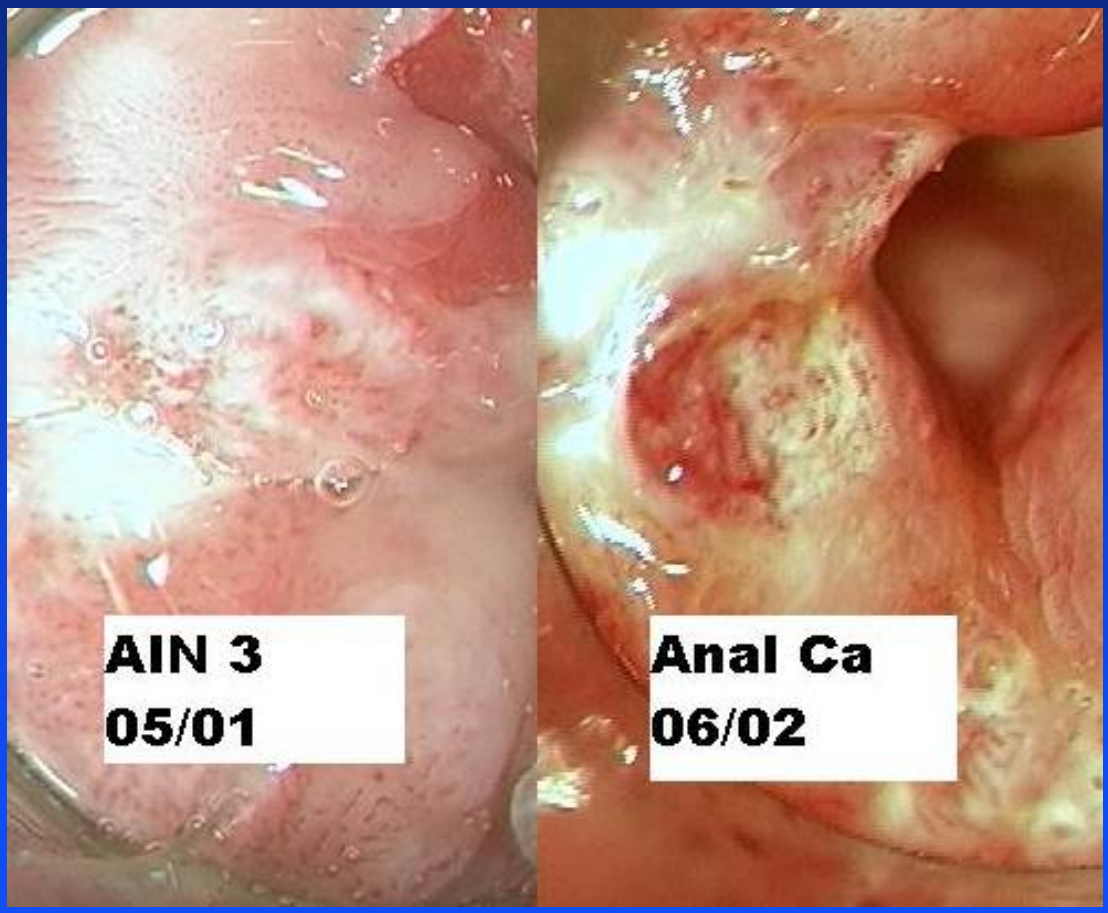
Daling JR et al. *Cancer*. 2004;101:270-289.
Holly EA et al. *J Natl Cancer Inst.* 1989;81:1726-31.

Risk factors for anal cancer

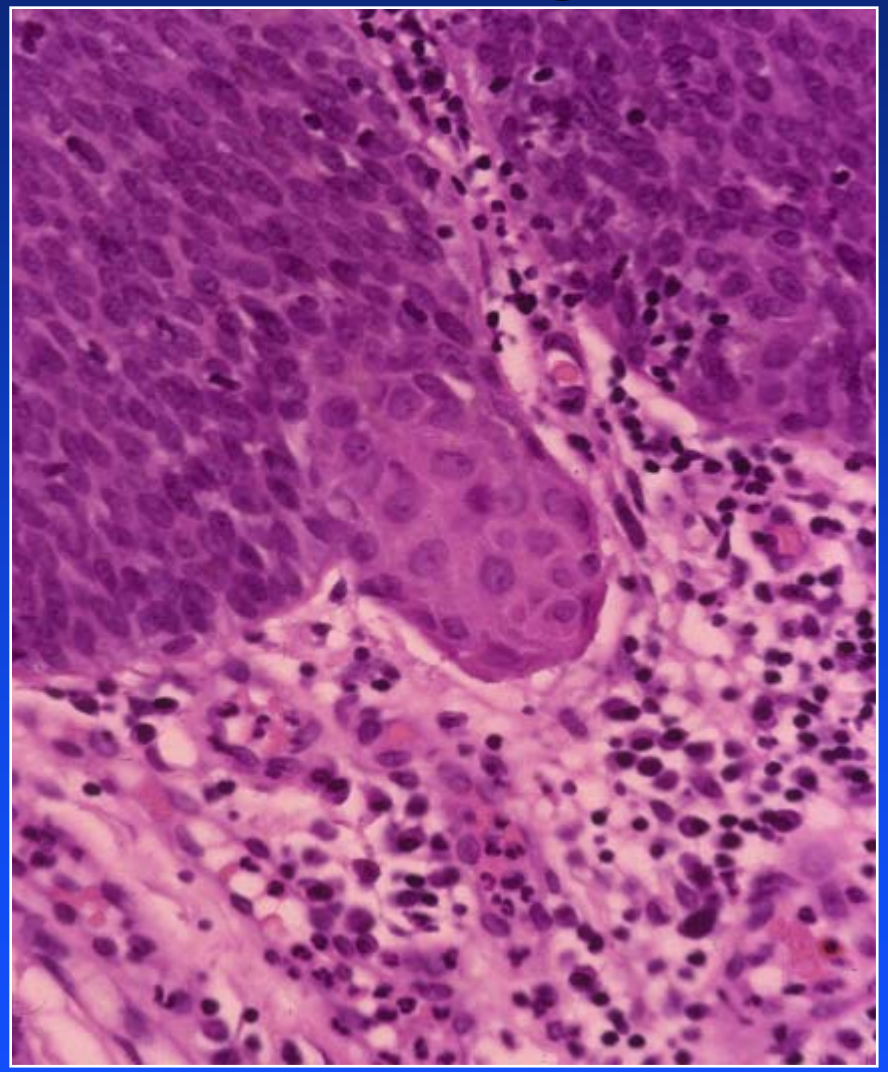
- Immunosupppression
  - HIV infection
  - Iatrogenic immunosuppression to prevent solid organ transplant
  - Diabetes
- Other HPV-related cancers- cervix and vulva

Palefsky JM et al. *Obstet Gynecol Clin N Am*. 2009;36:187-200.

AIN 2/3 is the precursor to anal cancer



Superficially invasive anal cancer arising from AIN 2/3



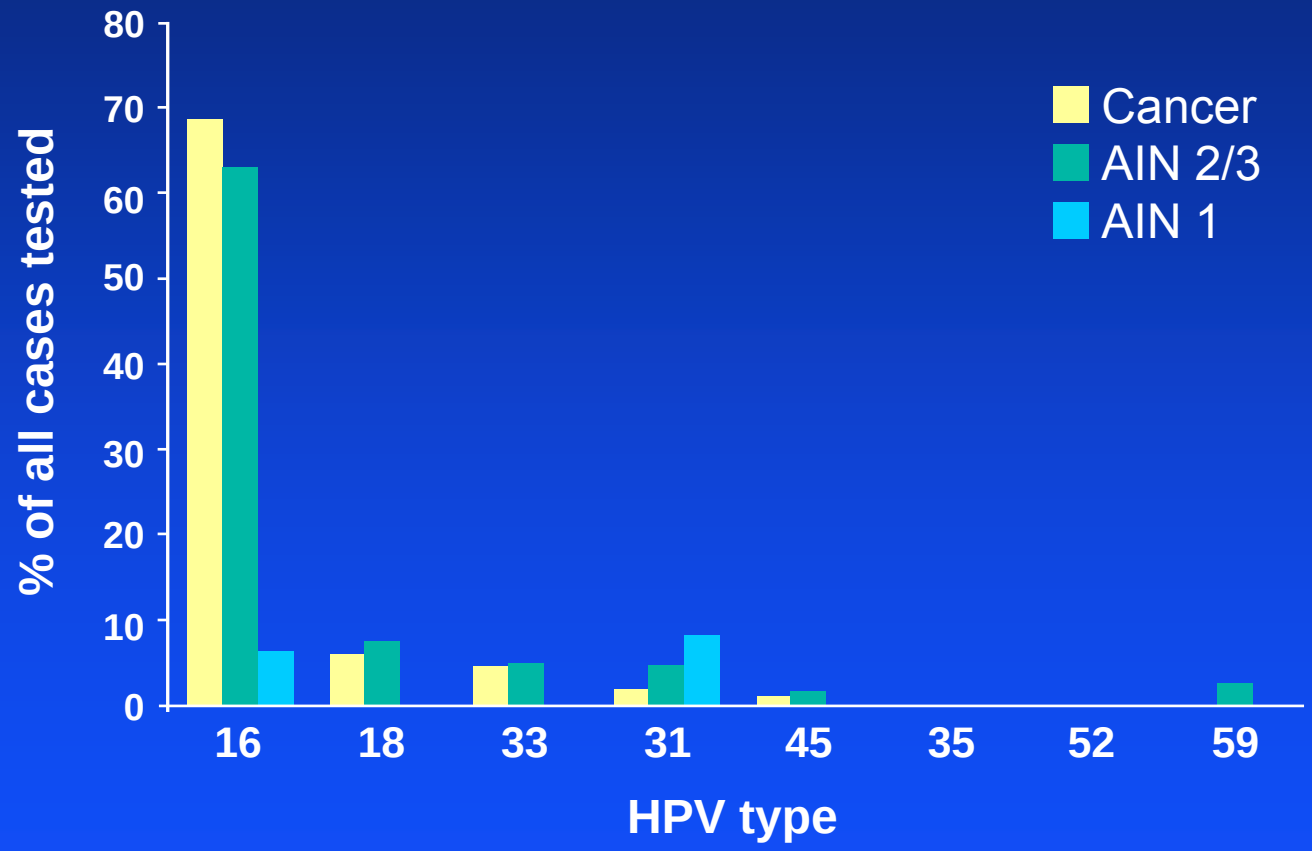
AIN 2/3 is the precursor to anal cancer

- Classic Bowen's (peri-anal AIN 2/3): 5-10% progression
  Rickert RR et al. *CA*. 1977; 27:160-6
- 3 of 6 (50%) immunosuppressed patients progressed from AIN 2/3 to cancer over 5 years
  Scholefield JH et al. *Br J Surg*. 2005;92:1133-6

AIN 2/3 is the precursor to anal cancer

- 8 of 55 (15%) immunosuppressed patients (men and women) progressed from AIN 2/3 to cancer over 42 months
  Watson et al. *ANZ J Surg*. Aug 2006;76(8):715-17
- 21 patients (mostly men) with AIN 2/3 progressed to cancer over an average of 47 months from time of first diagnosis
  Palefsky and Berry, unpublished data

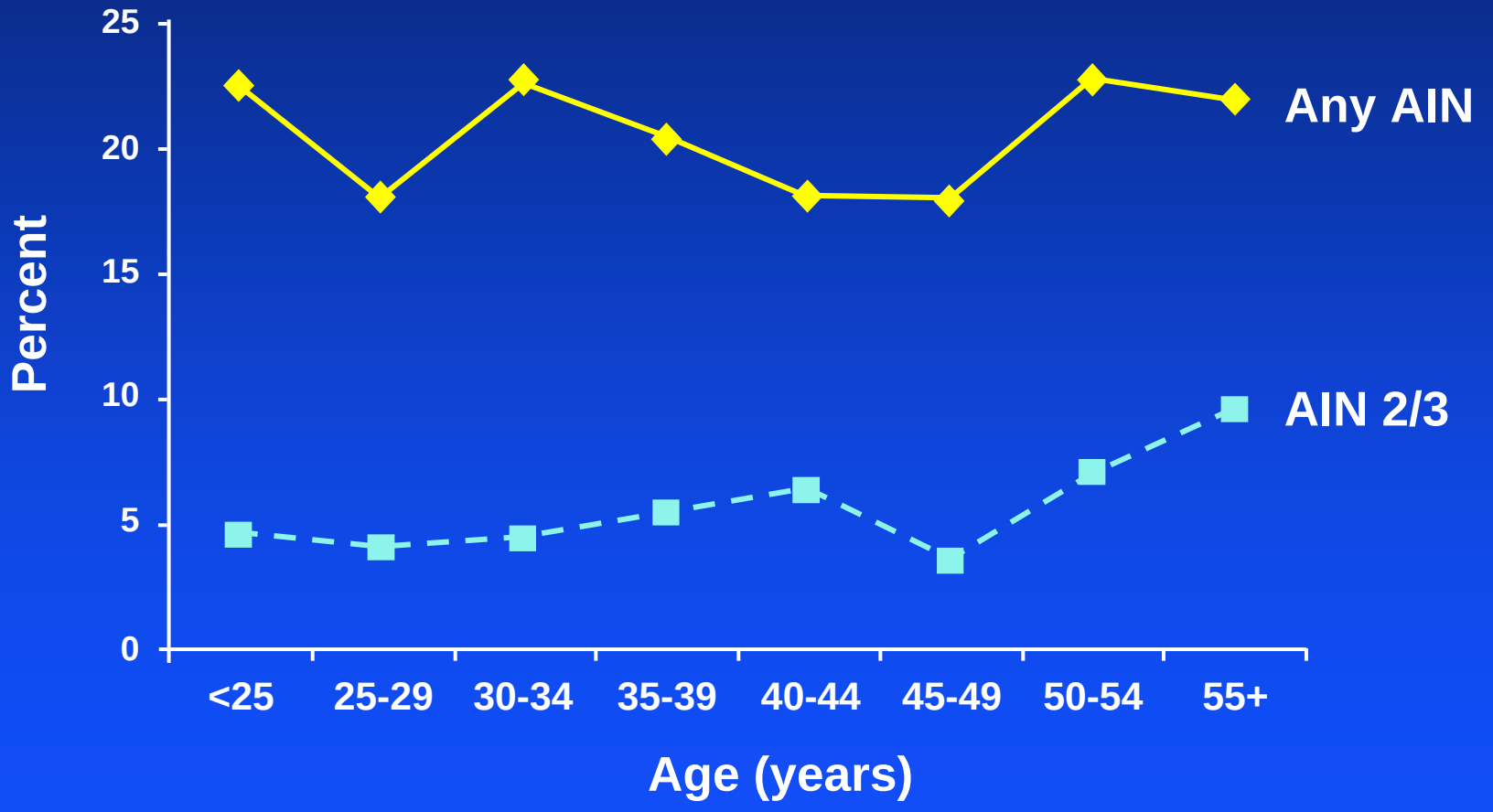
AIN 2/3 has the same HPV types as anal cancer



Hoots, BE et al. *Int J Cancer*. 2009;124:2375-2383.

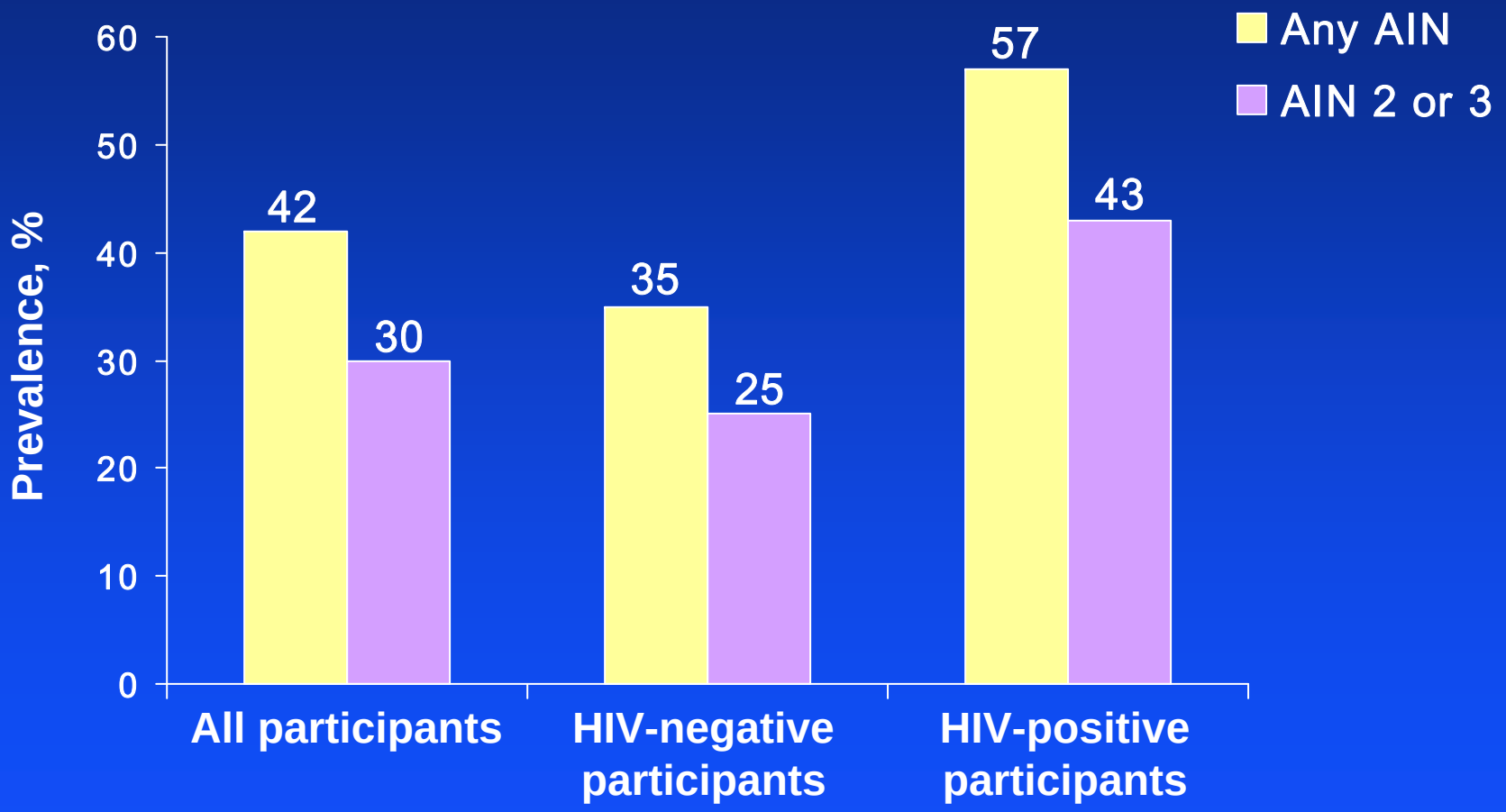
Prevalence and incidence of AIN 2/3

Prevalence of anal cytologic abnormalities by age among sexually active HIV-negative MSM



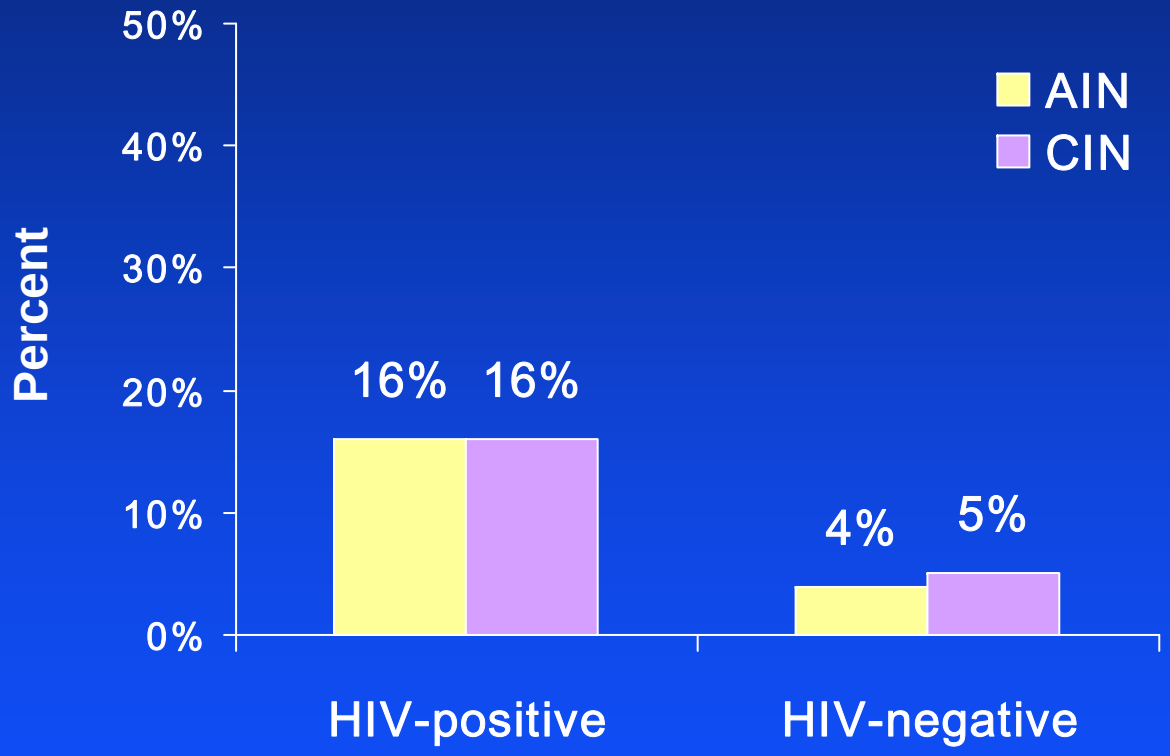
Chin-Hong PV et al. *J Natl Cancer Inst*. 2005;97:896-905.

Prevalence of AIN among MSM
Population-based data



Chin-Hong et al. *Ann Int Med.* 2008;149;300-6.

AIN in HIV-positive and HIV-negative women in the Women's Interagency HIV Study (N=657)



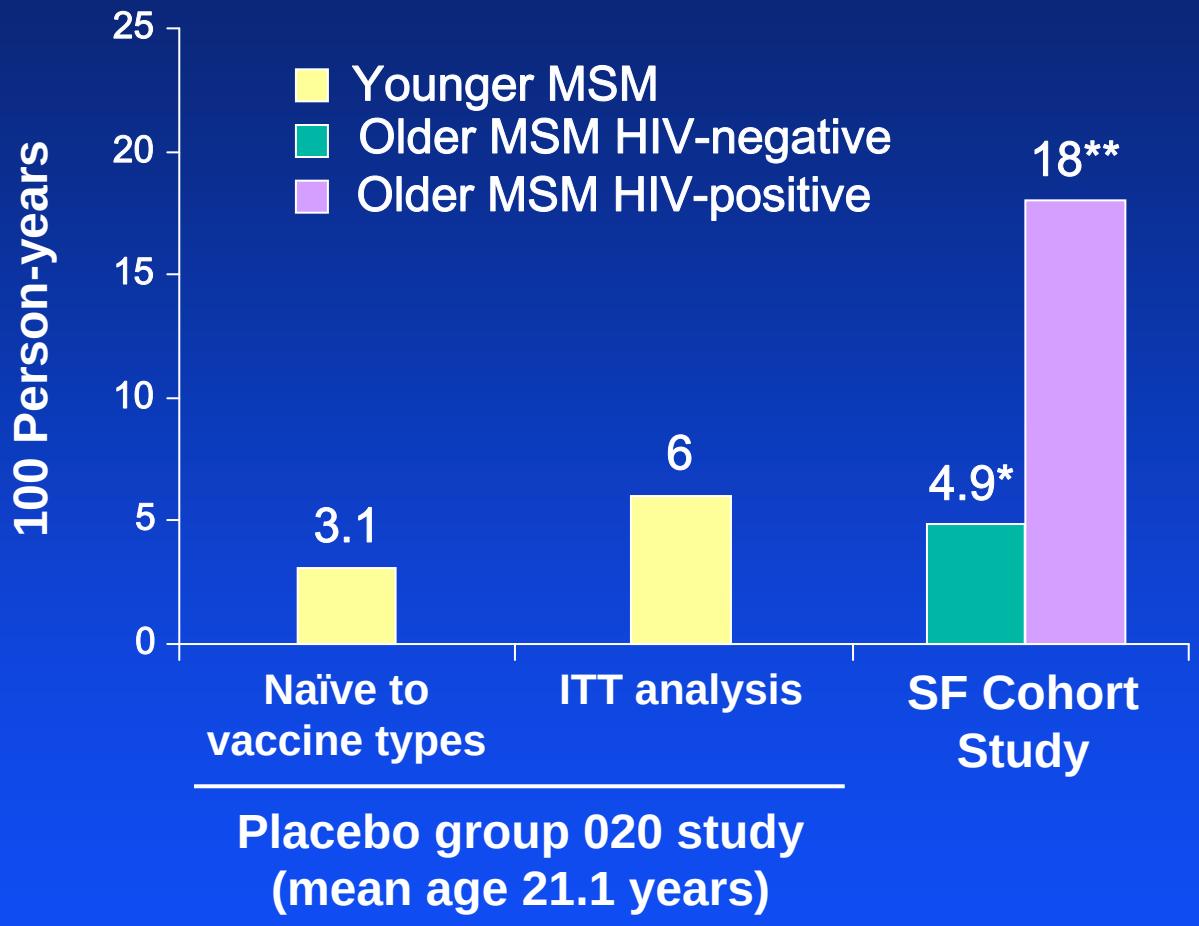
Hessol NA et al. *AIDS*. 2009;23:59-70.

AIN in women with CIN/VIN/VAIN

- Of 205 patients with genital intraepithelial neoplasia, 12.2% (95% CI 8- 17%) had AIN including 8% with AIN 2/3 (5 AIN 2 and 12 AIN 3)

Santoso JT et al. Obstet Gynecol 2010;116:578–82

Incident AIN 2/3 among MSM



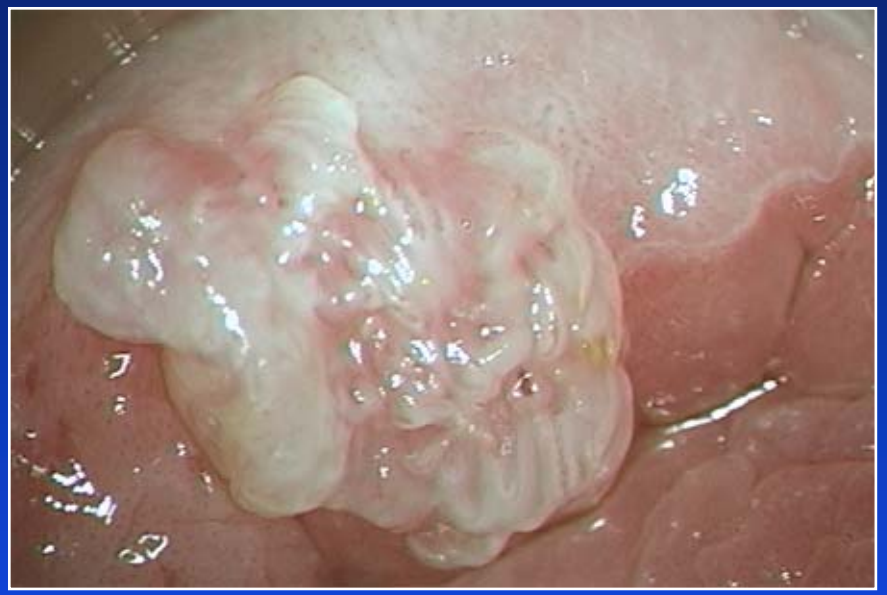
*Mean age 42 years. **Mean age 45 years.

Palefsky, Giuliano et al, submitted for publication.

Palefsky et al. *AIDS*. 1998,12:495–503.

Anogenital condyloma

- Approximately 90% of anogenital warts contain HPV 6 and HPV 11 DNA.[1]
- Anogenital warts are common[2] and highly contagious[3]:
  - 4% of sexually active men 18 to 59 years of age have ever been diagnosed with genital warts.[2]
  - >75% of sexual partners develop warts when exposed.[3]
- 3% to 24.9% of HIV-positive individuals have anal warts.[4]
- Symptoms may include[5]:
  - Itching, burning, bleeding and tenderness at the wart site



- Treatment can be painful, embarrassing, and expensive, and may not prevent recurrence.[5–7]

1. Gissmann L et al. *Proc Natl Acad Sci USA*. 1983;80(2):560-563. 2. Dinh T-H et al. *Sex Transm Dis*. 2008;35(4):357-360. 3. Soper DE. In: Berek JS, ed. *Novac's Gynecology.* 13th ed. 2002:453-470. 4. Vukasin P. *Surg Clin North Am*. 2002;1199-1211. 5. Insinga RP et al. *Clin Infect Dis*. 2003;36(11):1397-1403. 6. Maw RD et al. *Int J STD AIDS*. 1998;9(10):571-578. 7. Kodner CM et al. *Am Fam Physician*. 2004;70(12):2335-2342.

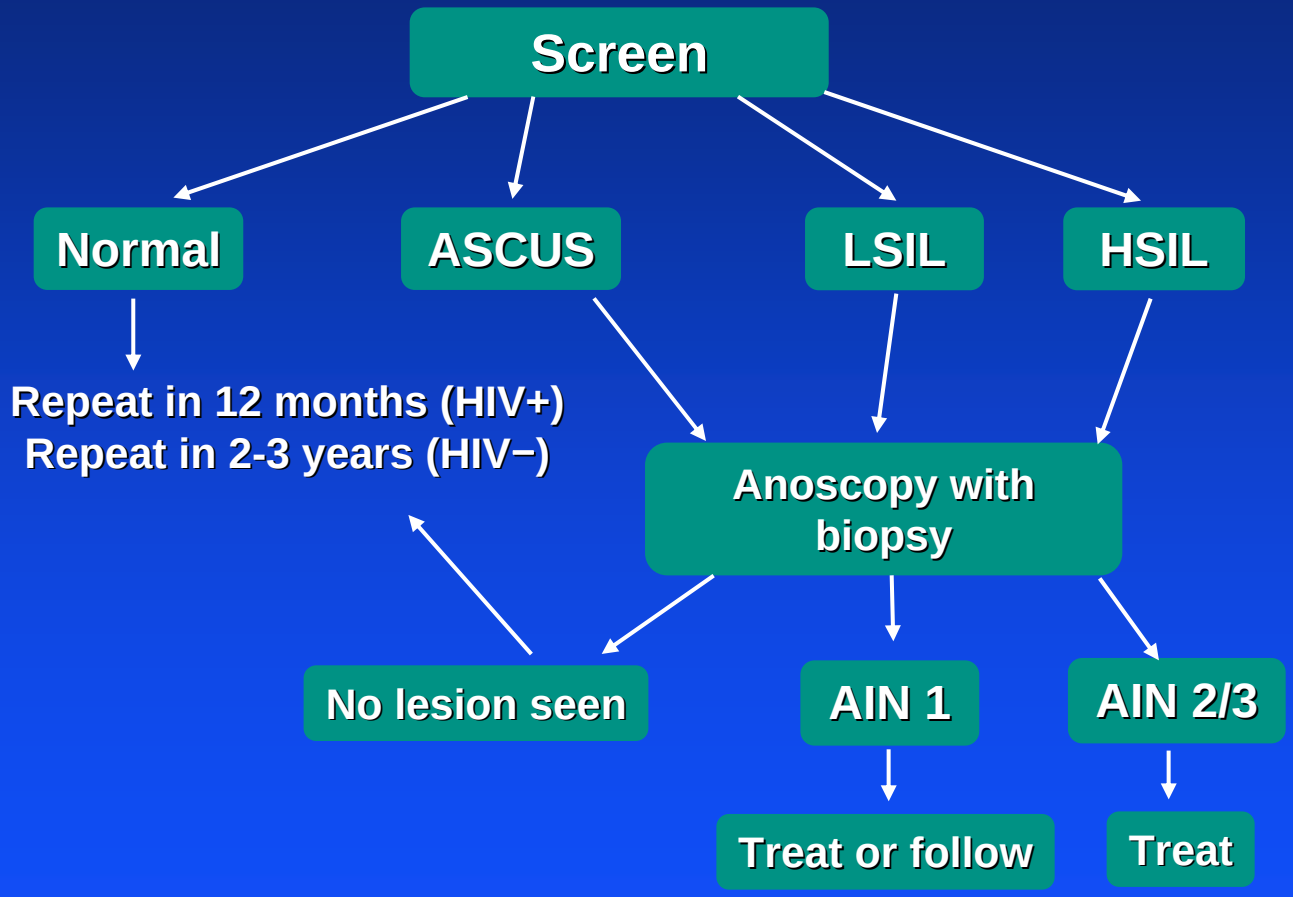
What should we do?

University of California San Francisco

Anal Neoplasia Clinic

- Screen for AIN using anal cytology
- Visually identify using high resolution anoscopy and biopsy anal lesions to confirm AIN 2/3 and exclude cancer
- Treat AIN 2/3

Anal cytology screening for AIN



Chin-Hong PV et al. *J Infect Dis.* 2004;90:2070-2076.

Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM over the age of 40 years
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients

Treatment of AIN 2/3

- Challenging due to multifocal nature, size of lesions
- Multiple procedures often needed
- High recurrence rate and incidence of new lesions
- Therapy is ablative
  - infra-red coagulation
  - 85% trichloroacetic acid

Reasons for lack of routine anal screening

- Paucity of clinicians trained in high resolution anoscopy, biopsy and AIN treatment
- Lack of evidence that treatment of AIN 2/3 prevents anal cancer

Conclusions

- Anal cancer is the same disease as cervical cancer
- AIN 2/3 is the same disease as CIN 2/3 and is the anal cancer precursor
- Anal cancer and AIN 2/3 are the same in men and women
- Anal cancer is a growing problem in the general population and in select risk groups

Conclusions

- Anal HPV is remarkably common in all segments of the population
- AIN 2/3 is common in select risk groups
- Treatment of AIN 2/3 is challenging
- Screening for AIN is not standard of practice
- Alternative methods to prevent anal cancer are needed

Agenda

- Joel Palefsky, MD
  - Anal HPV infection, AIN and anal cancer
- Patrick Brill-Edwards, MD
  - Current status of GARDASIL®
  - Proposed indication
- Elizabeth Garner, MD, MPH
  - The role of HPV in anal cancer in men and women
  - The burden of anal cancer in men and women
  - High-grade anal intraepithelial neoplasia (AIN 2/3): the precursor of anal cancer
  - AIN study design and results
  - Postlicensure surveillance and longer term studies
  - Rationale for an anal cancer indication in males and females

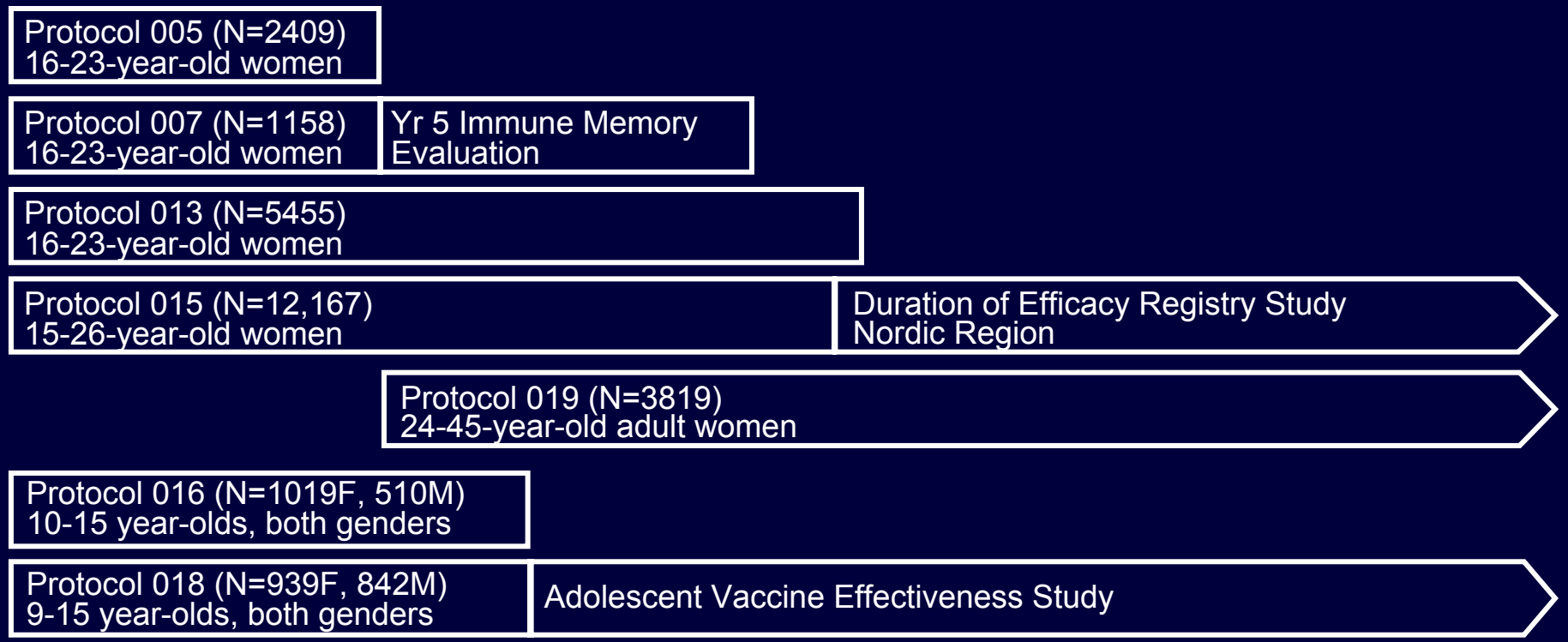
GARDASIL®
Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine

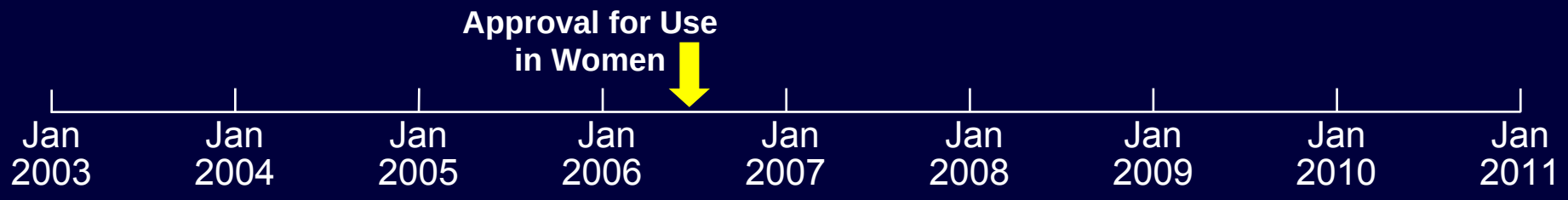
Constituent	L1 VLP				Merck's Aluminum Adjuvant†
	HPV 6	HPV 11	HPV 16	HPV 18	
Dose (µg)	20	40	40	20	225

- Merck's adjuvant has been used for more than 20 years
- VLPs manufactured in *Saccharomyces cerevisiae* (yeast)
- The VLPs are not viruses, so cannot cause infection or disease

† Merck's aluminum hydroxyphosphate sulphate.
HPV = human papillomavirus.

Clinical Program for GARDASIL®





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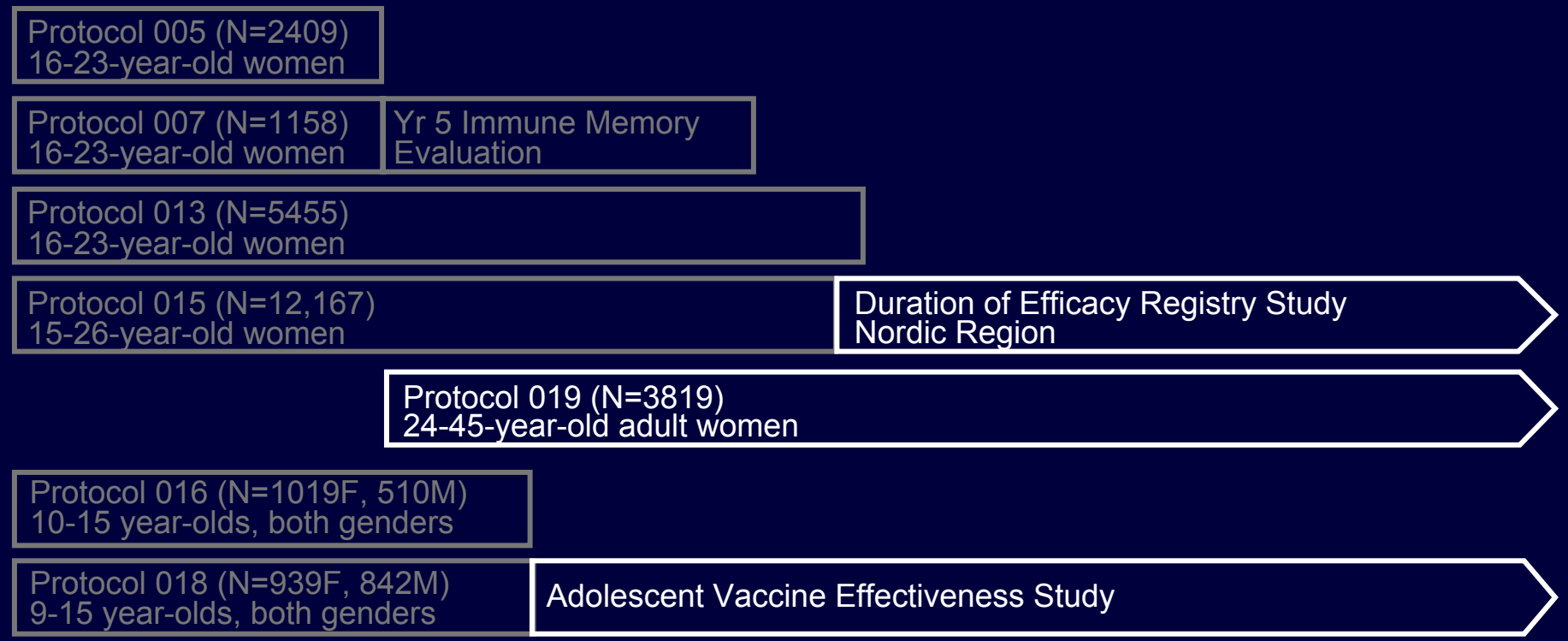

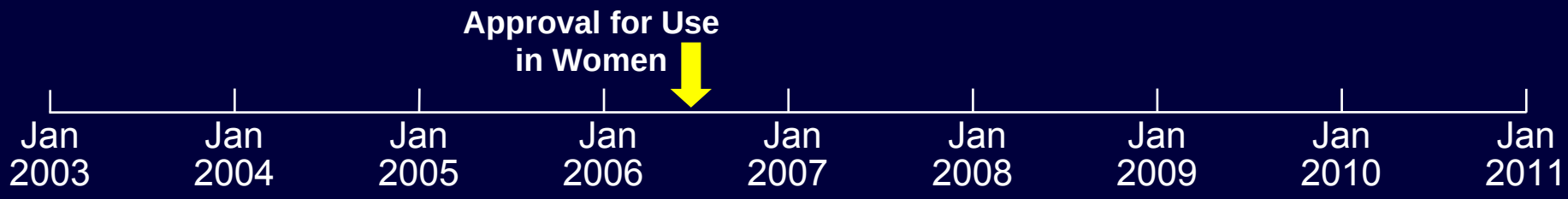

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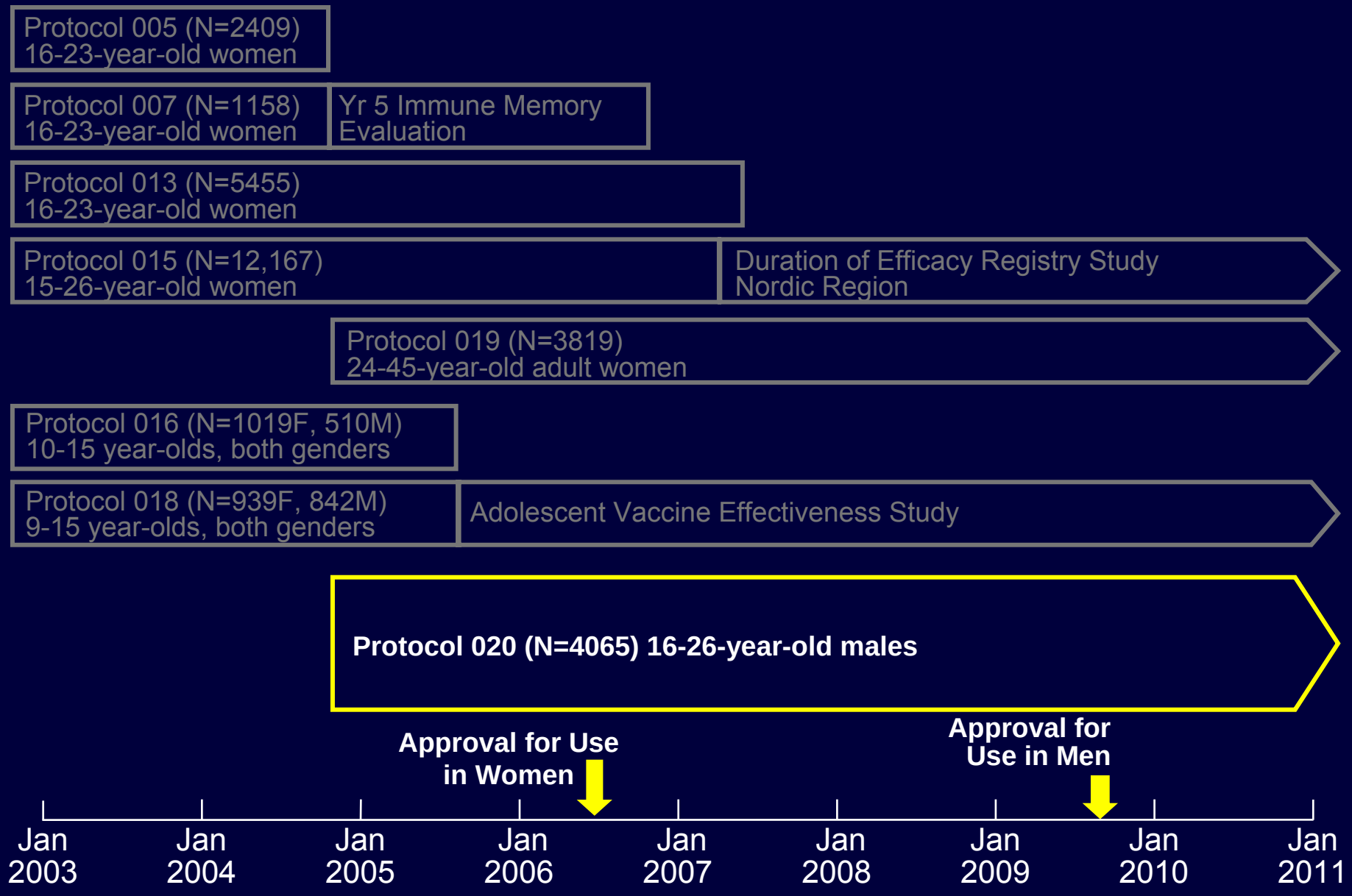
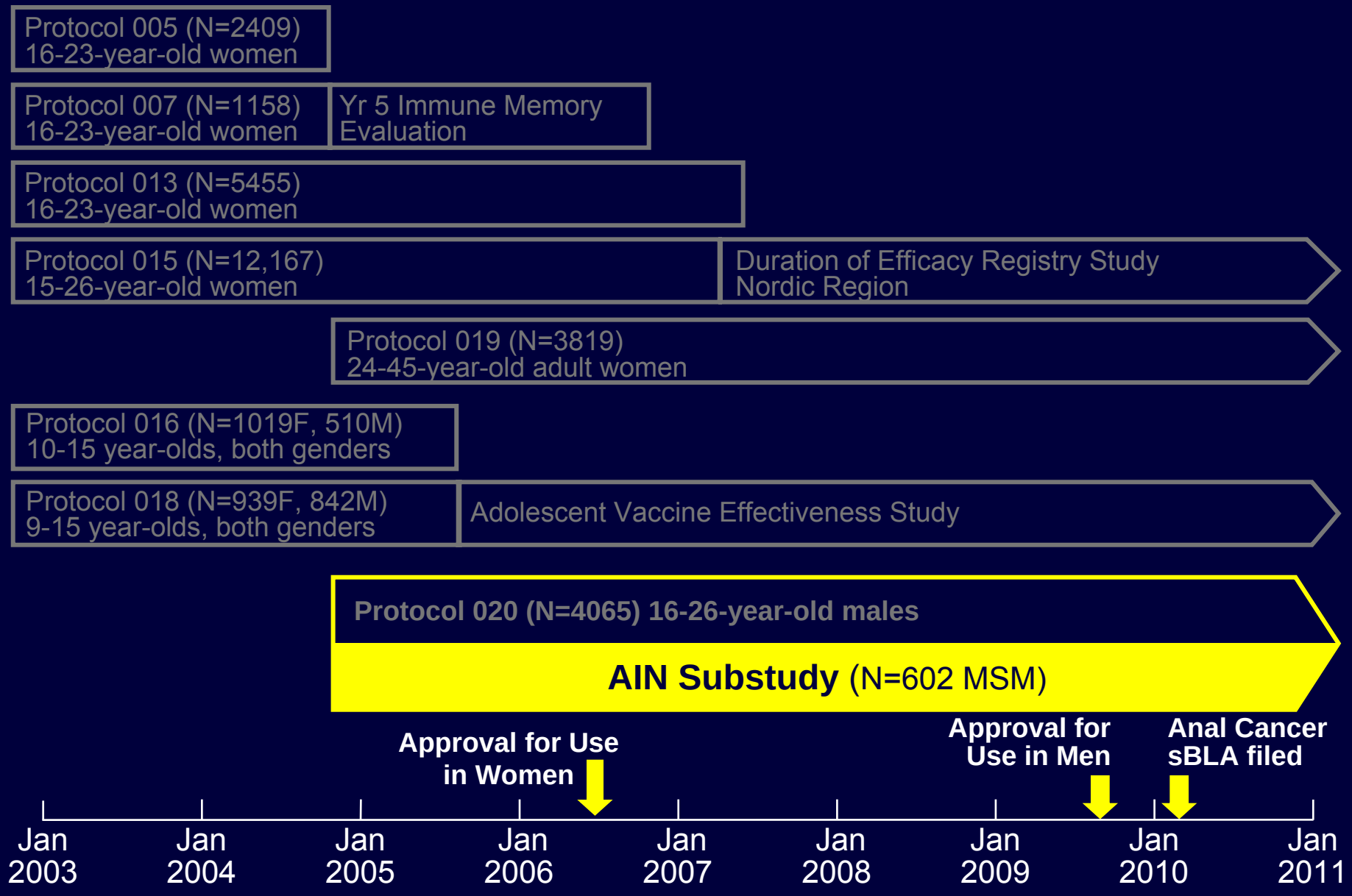


Clinical Program for GARDASIL®



Consistent Efficacy of GARDASIL® in the Genital Tracts of Young Men and Women

Population	HPV 6/11/16/18-Related Endpoints	Per Protocol Efficacy (%)	95% CI
16-26 year-old women	CIN 2/3	98	94, 100
	VIN 2/3	100	67, 100
	VaIN 2/3	100	55, 100
	Genital warts	99	96, 100
16-26 year-old men	Genital warts	90	65, 98

There is an Unmet Medical Need to Prevent Anal Cancer

- Up to 90% of anal cancer is caused by HPV
- Anal cancer is more common in women than men, but the incidence is rising in both groups
- Anal cancer treatment, even when successful is associated with substantial morbidity

HPV = human papillomavirus.

GARDASIL® Helps Address This Unmet Medical Need

- Currently there is no vaccine approved for prevention of HPV-related anal precancers or cancer
- The AIN study builds upon the high efficacy previously demonstrated across all evaluated genital endpoints in men and women
- In males, the end-of-study results confirm the established favorable safety profile of GARDASIL
- Given the totality of the data, the AIN study extends the potential benefit of GARDASIL to anal cancer prevention in both men and women

HPV = human papillomavirus; AIN = anal intraepithelial neoplasia.

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  - Anal HPV infection, AIN and anal cancer
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  - Current status of GARDASIL®
  - Proposed indication
- Elizabeth Garner, MD, MPH
  - The role of HPV in anal cancer in men and women
  - The burden of anal cancer in men and women
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Proposed Indication (Girls and Women)

1.1 GARDASIL® is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal **and anal** cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

  And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- **Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3**

Proposed Indication (Boys and Men)

1.2 Boys and Men

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- **Anal cancer caused by HPV types 16 and 18**
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

  And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- **Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3**

HPV = human papillomavirus.

Basis for Proposed Indication

- The proposed indication is based upon disease endpoints
- Anal cancer is the same disease in men and women
- Most anal cancer is caused by HPV
- AIN 2/3 is the precursor of anal cancer
- Preventing AIN 2/3 will prevent anal cancer
- The benefit/risk profile continues to be favorable

HPV = human papillomavirus; AIN = anal intraepithelial neoplasia.

Consultants

Catherine Dean, MD	Washington University School of Medicine
Anna Giuliano, PhD	H. Lee Moffitt Cancer Center and Research Institute
Joel Palefsky, MD	University of California, San Francisco
Mark Stoler, MD	University of Virginia
Lee-Jen Wei, PhD	Harvard University

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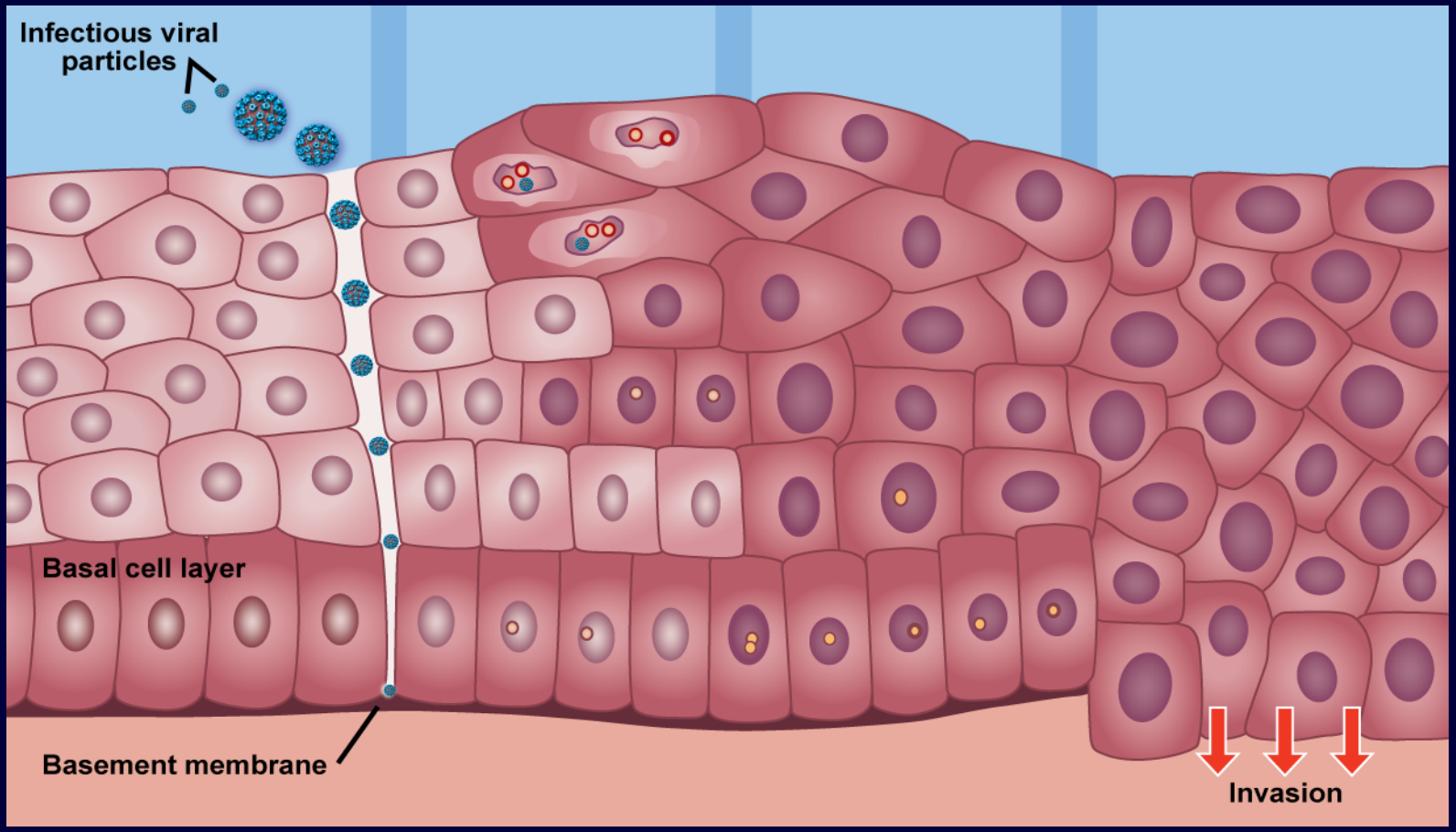
Human Papillomavirus (HPV) is a Potent Carcinogen

- Non-enveloped double-stranded DNA viruses
- >100 types identified
- ~30-40 types sexually transmitted
- Classified as low- and high-risk types[1]
- High lifetime risk of HPV-related pathology
- The four HPV types prevented by GARDASIL® (6, 11, 16 and 18) together cause the majority of HPV-related benign and malignant disease in the anogenital tracts of men and women

[1] Munoz N, NEJM 2003.

HPV-Related Cancers Have a Similar Path to Development

Initial Infection → Persistent Infection → IN 2/3 → Invasive carcinoma



HPV = human papillomavirus; IN=Intraepithelial Neoplasia.

HPV Causes Multiple Related Cancers in Men and Women

Estimated Number of New Cases – USA, 2010[1,2]

Cancer Site	New Cases	% Detectable HPV[3]	New HPV-Related Cases Per Year
Cervix	12,200	100	12,200
Vulva	3900	40	1560
Vagina	1100	40	440
Penis	980	40	392
Oral Cavity/Oropharynx	36,500	25	9135
Anus	5260	90	4734
Total cancers			28,461

[1]SEER Fact Sheet NCI 2010; [2]CDC and NCI 2010; [3]Watson, M, Cancer Suppl 2008.
HPV = human papillomavirus.

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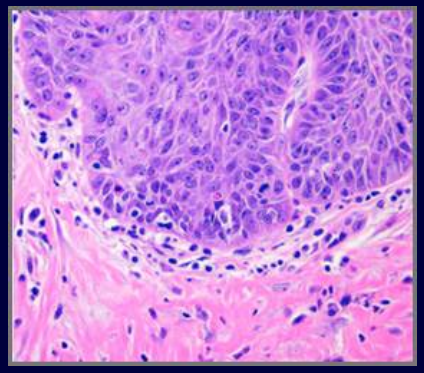
Anal Cancer is Analogous to Cervical Cancer

- Risk factors for anal and cervical cancer are similar[1,2]
- Anal cancers arise in the transformation zone of the anal canal[3]
- Histology and molecular characteristics are similar to cervical cancer[4,5]

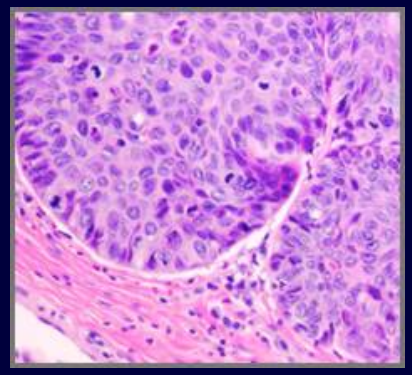
[1]Palefsky JM, Obstet Gynecol Clin N Am 2009; [2]Frisch M, NEJM 1997; [3]Ryan DP, NEJM 2000; [4]Haga T, JAIDS 2001; [5]Little VR, Dis Colon Rectum 2000.

Anal Cancer is the Same Disease in Men and Women

- Causal HPV types are the same in men and women[1]
- HPV-related anal cancers arise in the same anatomic location and cell type in men and women
- Molecular characteristics are the same between the genders
- Anal cancers in men and women are histologically indistinguishable



Anal Cancer in a Male



Anal Cancer in a Female

[1]Hoots BE, IJC 2009; Photographs Courtesy of M. Stoler, M.D.
HPV = human papillomavirus.

Risk Factors for Anal Cancer Are the Same in Men and Women

- Populations in which risk factors are more prevalent have higher incidences of anal cancer[1,2]
  - Lifetime number of sexual partners positively correlated with risk of anal cancer[3,4]
- Anal intercourse is a risk factor but is not required for anal HPV infection or cancer development in men or women[3-7]

Proportion of Men and Women with Anal Cancer who Reported No History of Anal Intercourse[3-7]

Females (N=891)	Males (N=311)	Heterosexual Males (N=200)	Men Who Have Sex With Men (N=111)
68-86%	59-92%	100%	13-50%

N=total number of subjects with anal cancer among all 5 studies combined.
[1]Scholefield JH, BrJSurg 1994; [2]Sobhani I, AIDS 2004; [3]Daling JA, Cancer 2004; [4]Frisch M, NEJM 1997; [5]Frisch M, Cancer Res 1999; [6]Daling JA, NEJM 1987; [7]Holly EA JNCI 1989.
HPV = human papillomavirus.

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The Burden of Anal Cancer is Increasing

- Annual Burden of Anal Cancer in the United States[1]
  - 5260 new cases
  - 720 deaths
  - ~60% of cases and deaths occur in women[1]
  - Among men, a substantial proportion of cases occur in heterosexual men[2]
- Incidence is increasing at ~2% per year[3]
- Deaths due to anal cancer are increasing at ~1.7% per year[3]

[1]SEER Fact Sheets NCI 2010; [2]Daling J, Cancer 2004; [3]SEER Fast Stats 1992-2007 NCI 2010.

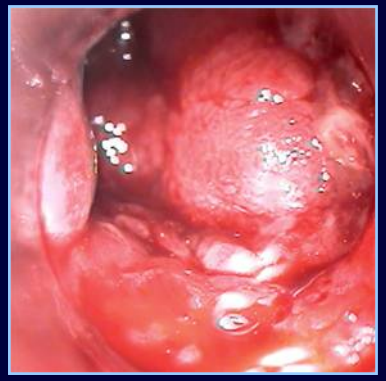
Prevention of Anal Cancer is an Unmet Medical Need

- Anal HPV infection that can lead to cancer is common in men and women and not easily prevented[1,2]
- ~40% of patients are diagnosed with regional or distant spread of disease[3]
- Screening of the general population is not practical

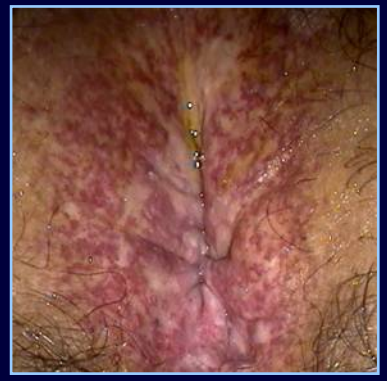
[1]Nyitray AG, JID 2010; [2]Goodman MT, JID 2010; [3]Joseph DA, Cancer 2008.
HPV = human papillomavirus.

Treatment of Anal Cancer Has Significant Side Effects

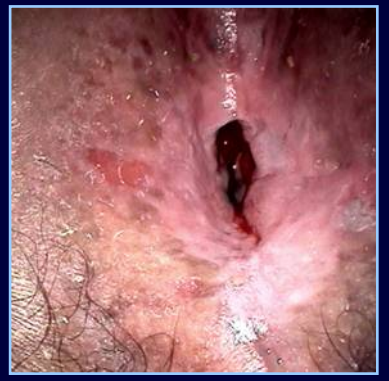
- Treatment consists primarily of radiation and chemotherapy[1]
- Radiation therapy is associated with acute and chronic morbidity and negatively impacts many aspects of quality of life[2]
- Late radiation effects or disease recurrence may necessitate colostomy in 6-12% of patients[1]



Radiation proctitis



Radiation-related skin inflammation



Post-radiation anal stenosis

[1]Ryan DP, NEJM 2000; [2]Das P, Cancer 2010; Photographs Courtesy of S. Goldstone, M.D.

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AIN 2/3 is the Precursor of Anal Cancer

- Individuals with AIN 2/3 have a substantially elevated risk of invasive anal cancer[1-4]
  - Natural history studies also point to limitations of AIN treatment
- Molecular and histologic evidence support the epidemiology data[5]
  - Histologic progression observed in lesions
  - AIN and anal cancer share molecular changes
- Expert groups recognize high-grade AIN as the precursor of anal cancer

[1]Sobhani I, AIDS 2004; [2]Scholefield JH, Br J Surg 2005; [3]Watson AJM, ANZJ S 2006;
[4]Kreuter A, Br J Dermatol 2010; [5]Wong AK, Mod Pathol 2010.
AIN = anal intraepithelial neoplasia.

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Rationale for the GARDASIL® Clinical Development Program

- GARDASIL is a prophylactic vaccine
- Efficacy is highest when administered prior to sexual debut
- Preadolescent boys and girls are the optimal age group for routine immunization
- Efficacy studies among preadolescents are not feasible – efficacy was studied in adults and bridged to preadolescents

The GARDASIL® Efficacy Study in Men Protocol 020

- Multinational, randomized (1:1), double-blind, placebo-controlled study
  - 3463 heterosexual men (HM) aged 16-23 years
  - 602 MSM aged 16-26 years
- Overall study evaluated:
  - Efficacy against external genital lesions (EGL), persistent infection and DNA detection
  - Immune responses
  - Safety

- Approval in 2009 for HPV 6/11-related genital warts in boys and men 9 to 26 years of age

MSM = men who have sex with men; DNA = deoxyribonucleic acid.

End of Study Results Were Consistent with Primary Analysis

- High efficacy against 6/11/16/18-related EGL
  - Primary analysis: 90% (95% CI: 69, 98)
  - End of study results: 91% (95% CI: 70, 98)
- Robust immune responses
- Favorable safety profile in HM and MSM
- Results are consistent with other pivotal clinical trials of GARDASIL®

EGL = external genital lesions; HM = Heterosexual men; MSM = men who have sex with men.

The AIN Substudy in MSM

- Predefined study within Protocol 020 aimed at evaluation of GARDASIL® efficacy against anal infection and disease
- N=602 Protocol 020 MSM subjects aged 16-26 years
- MSM subjects contributed to overall study endpoints
- MSM selected due to high incidence rates of anal HPV infection and disease
  - This approach allowed efficacy demonstration within reasonable study timelines

AIN = anal intraepithelial neoplasia; MSM = men who have sex with men; HPV = human papillomavirus.

Evaluation of GARDASIL® Efficacy Against AIN

- Key inclusion criteria:
  - No history of HPV infection or disease
  - ≤5 lifetime sexual partners
  - HIV negative
- Subjects were followed for up to 36 months
  - Median follow-up: 32.2 months after Dose 1
- Objective: Among MSM, assess efficacy against combined incidence of HPV 6/11/16/18-related AIN or anal cancer
  - Analysis to be conducted when at least 17 cases of HPV 6/11/16/18-related AIN/anal cancer observed

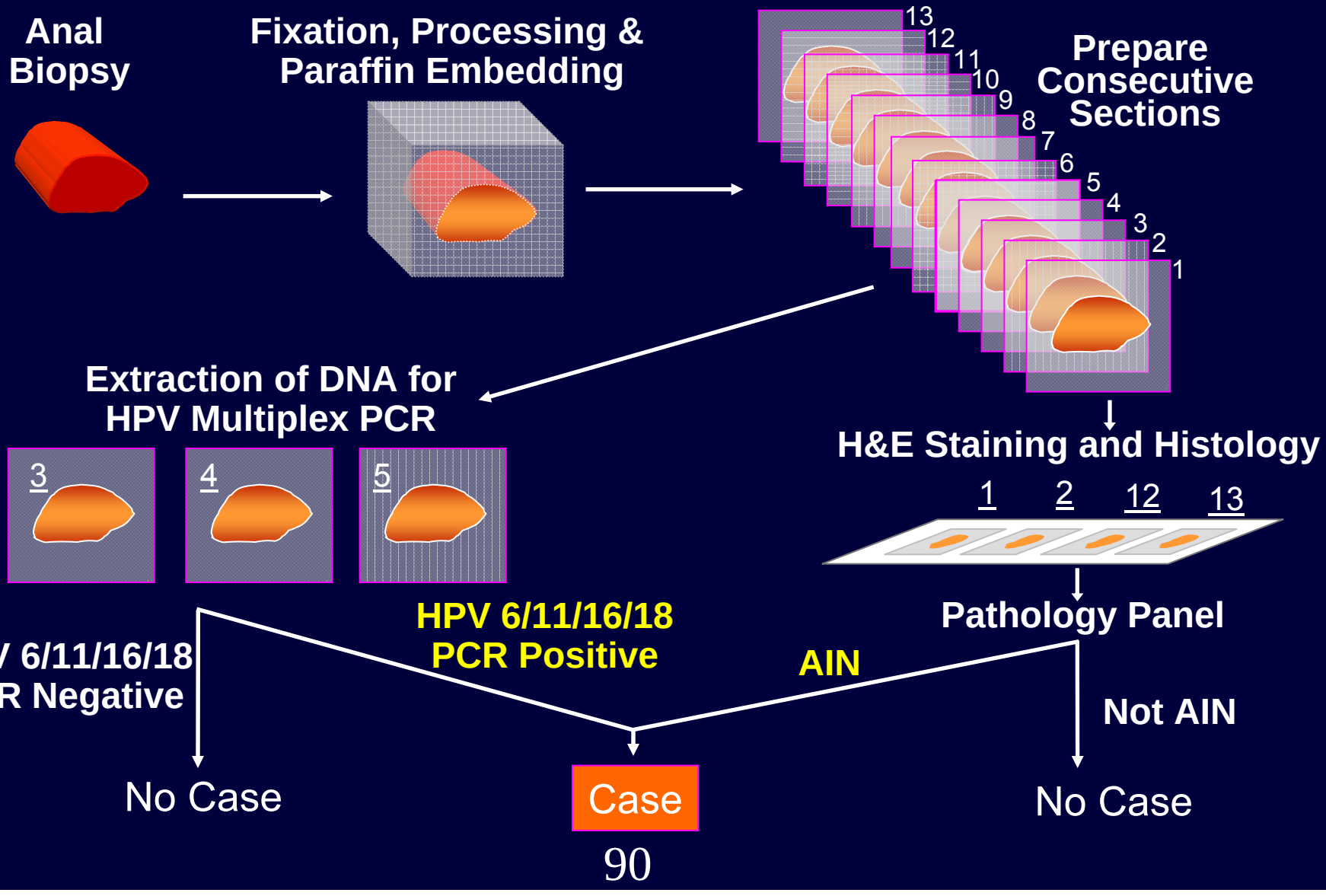
AIN = anal intraepithelial neoplasia; HPV = human papillomavirus; HIV = human immunodeficiency virus. MSM = men who have sex with men.

Rigorous Assessment of Anal Infection and Disease

- Anal swab sampling for HPV DNA detection by PCR
  - HPV+ if swab PCR+ for the relevant HPV type
- Anal cytology
  - Protocol-specified cytology management algorithm
- High-resolution anoscopy (HRA)/intra-anal biopsy
  - Evaluation of abnormal cytology
  - Mandatory HRA at final study visit

HPV = human papillomavirus; DNA = deoxyribonucleic acid; PCR = polymerase chain reaction.

Consistent Methods Throughout GARDASIL® Clinical Program



Primary Prophylactic Efficacy Analysis Population

- Per-protocol efficacy (PPE) population
  - Received 3 doses of vaccine/placebo
  - Seronegative at Day 1; PCR negative at Day 1 and Month 7 to the relevant HPV type
  - HIV negative (MSM subjects tested yearly)
  - Endpoints were counted starting after Month 7

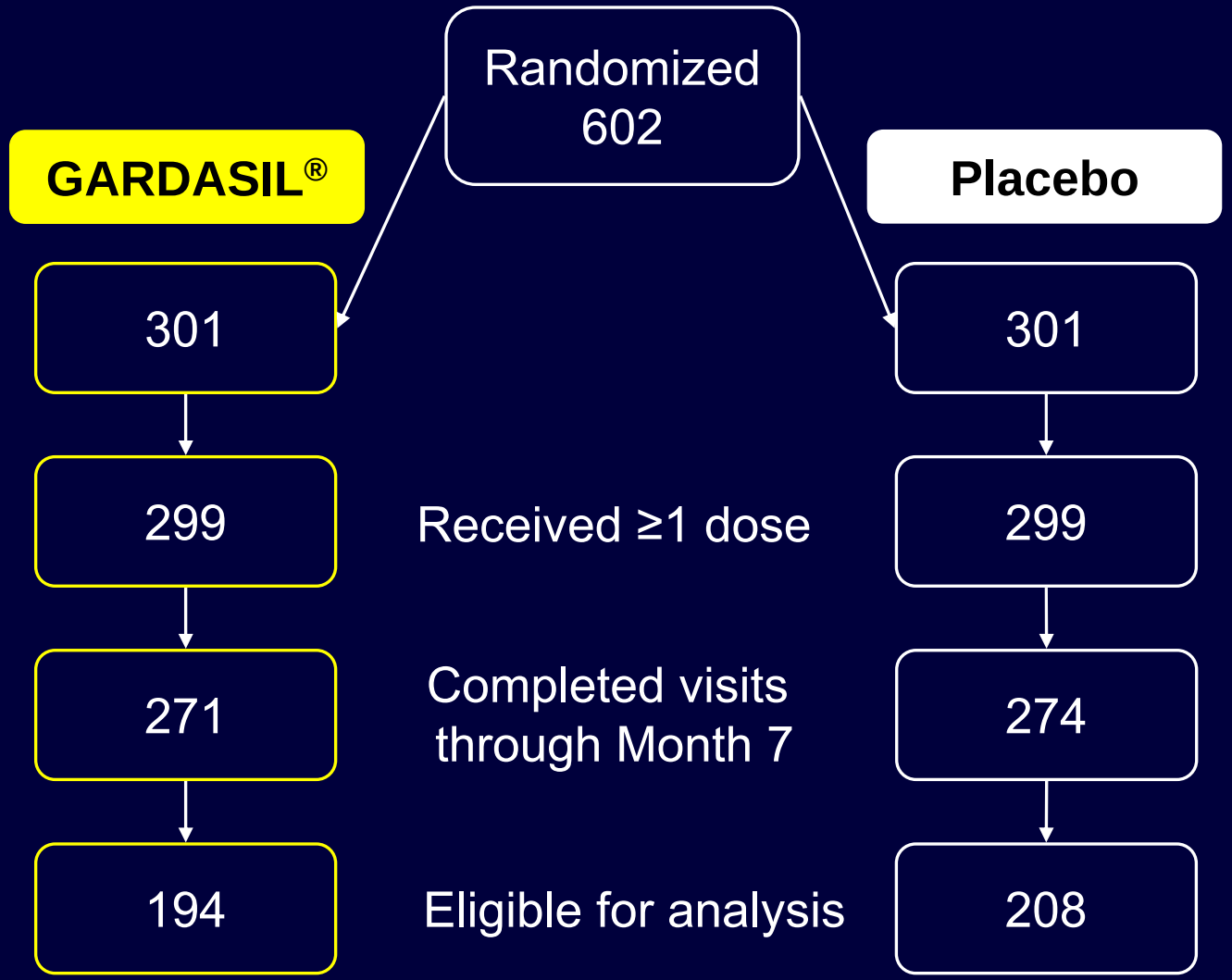
PCR = polymerase chain reaction; HPV = human papillomavirus; HIV = human immunodeficiency virus. MSM = men who have sex with men.

Supportive Intention-To-Treat Analysis Population

- Full analysis set (FAS)
  - Received ≥1 dose vaccine/placebo
  - Had follow-up after Day 1
  - Endpoints were counted starting after Day 1
  - Efficacy in FAS expected to be lower than in PPE

PPE = Per-protocol efficacy.

Subject Accounting for HPV 6/11/16/18 Per-Protocol Efficacy Analysis



HPV = human papillomavirus

Baseline Characteristics of Study Subjects

Characteristic	GARDASIL® (N=301)	Placebo (N=301)
Age, years		
Mean (SD)	22.2 (2.5)	21.1 (2.5)
Race/ethnicity		
Asian	15 (5%)	18 (6%)
Black	22 (7%)	20 (7%)
Hispanic American	72 (24%)	77 (26%)
White	185 (62%)	178 (59%)
Other	7 (2%)	8 (3%)

N = number of subjects randomized; SD = Standard deviation.

Efficacy Against HPV 6/11/16/18-Related Anal Intraepithelial Neoplasia (AIN)

Per-Protocol Efficacy Population

Endpoint	GARDASIL® Cases (n=194)	Placebo Cases (n=208)	% Efficacy	95% CI	p-Value

n = number of subjects in per-protocol population.
HPV = human papillomavirus; CI = confidence interval.

Efficacy Against HPV 6/11/16/18-Related Anal Intraepithelial Neoplasia (AIN)

Per-Protocol Efficacy Population

Endpoint	GARDASIL® Cases (n=194)	Placebo Cases (n=208)	% Efficacy	95% CI	p-Value
AIN or anal cancer	5	24	78	40, 93*	<0.001

*Multiplicity adjusted 95.1% CI; n = number of subjects in per-protocol population.
AIN includes AIN 1, 2, 3, and anal cancer.
HPV = human papillomavirus; CI = confidence interval.

Efficacy Against HPV 6/11/16/18-Related Anal Intraepithelial Neoplasia (AIN)

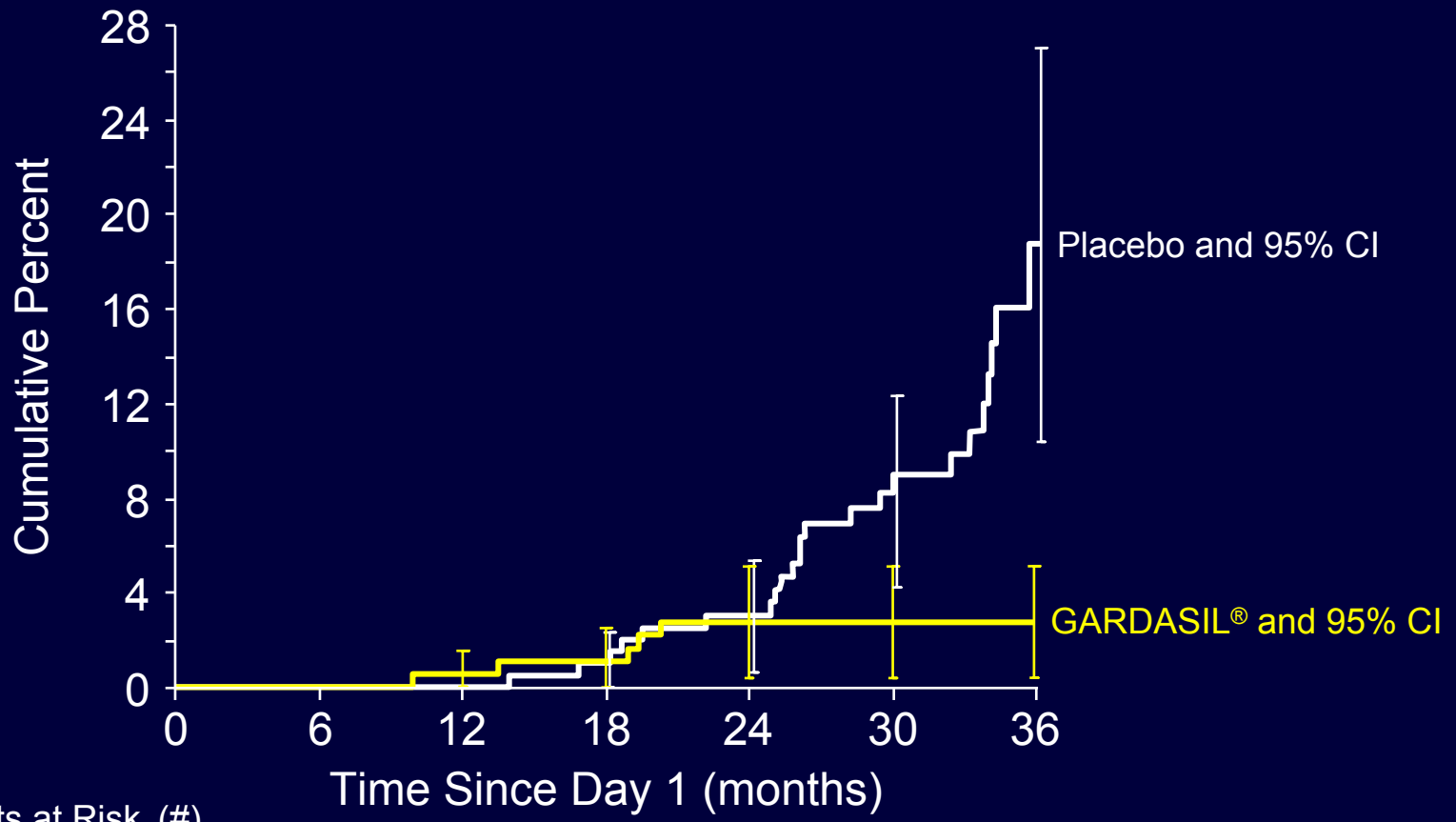
Per-Protocol Efficacy Population

Endpoint	GARDASIL® Cases (n=194)	Placebo Cases (n=208)	% Efficacy	95% CI	p-Value
AIN or anal cancer	5	24	78	40, 93*	<0.001
AIN 1	4	16	73	16, 93	
AIN 2/3	3	13	75	9, 95	
Anal cancer	0	0	NA	NA	

*95.1% CI for AIN 6/11/16/18; 95% CI for analyses by lesion type; n = number of subjects in per-protocol population; AIN includes AIN 1, 2, 3.
HPV = human papillomavirus; CI = confidence interval.

Time to Detection of HPV 6/11/16/18-Related AIN

Per-Protocol Efficacy Population



Subjects at Risk (#)							
GARDASIL	194	194	189	178	165	128	34
Placebo	208	208	206	199	178	130	29

HPV = human papillomavirus; AIN = anal intraepithelial neoplasia; CI = confidence interval.

Efficacy Against HPV 16/18-Related AIN 2/3

Per-Protocol Efficacy Population

Endpoint	GARDASIL® Cases (n=194)	Placebo Cases (n=208)	% Efficacy	95% CI
HPV 16/18-Related AIN 2/3	1	8	87	>0, 100

n = number of subjects in per-protocol population.
HPV = human papillomavirus; AIN = anal intraepithelial neoplasia; CI = confidence interval.

Efficacy Against HPV 6/11/16/18 Persistent Anal Infection

Per-Protocol Efficacy Population

	GARDASIL®		Placebo			
HPV Type	n	Cases	n	Cases	% Efficacy	95% CI
HPV 6/11/16/18	193	2	208	39	95	80, 99

Persistent infection: Detection of same vaccine type HPV DNA in ≥2 consecutive anogenital samples collected ≥6 months apart.
n = number of subjects in per-protocol population eligible for analysis.
HPV = human papillomavirus; CI = confidence interval.

Efficacy Against Persistent Anal Infection by HPV Type

Per-Protocol Efficacy Population

	GARDASIL®		Placebo			
HPV Type	n	Cases	n	Cases	% Efficacy	95% CI
HPV 6/11/16/18	193	2	208	39	95	80, 99
HPV 6	140	1	144	13	92	47, 100
HPV 11	140	0	144	5	100	<0, 100
HPV 16	166	1	170	16	94	60, 100
HPV 18	172	0	193	10	100	52, 100

Persistent infection: Detection of same vaccine type HPV DNA in ≥2 consecutive anogenital samples collected ≥6 months apart.
n = number of subjects in per-protocol population eligible for respective analysis.
HPV = human papillomavirus; CI = confidence interval.

Efficacy Against HPV 6/11/16/18-Related Anal Intraepithelial Neoplasia (AIN)

FAS Efficacy Population

Endpoint	GARDASIL® Cases (n=275)	Placebo Cases (n=276)	% Efficacy	95% CI
AIN or anal cancer	38	77	50	26, 67

n = number of subjects in FAS population with at least one follow-up visit after Day 1; AIN includes AIN 1, 2, 3.
HPV = human papillomavirus; FAS = full analysis set; CI = confidence interval.

Efficacy Against HPV 6/11/16/18-Related Anal Intraepithelial Neoplasia (AIN)

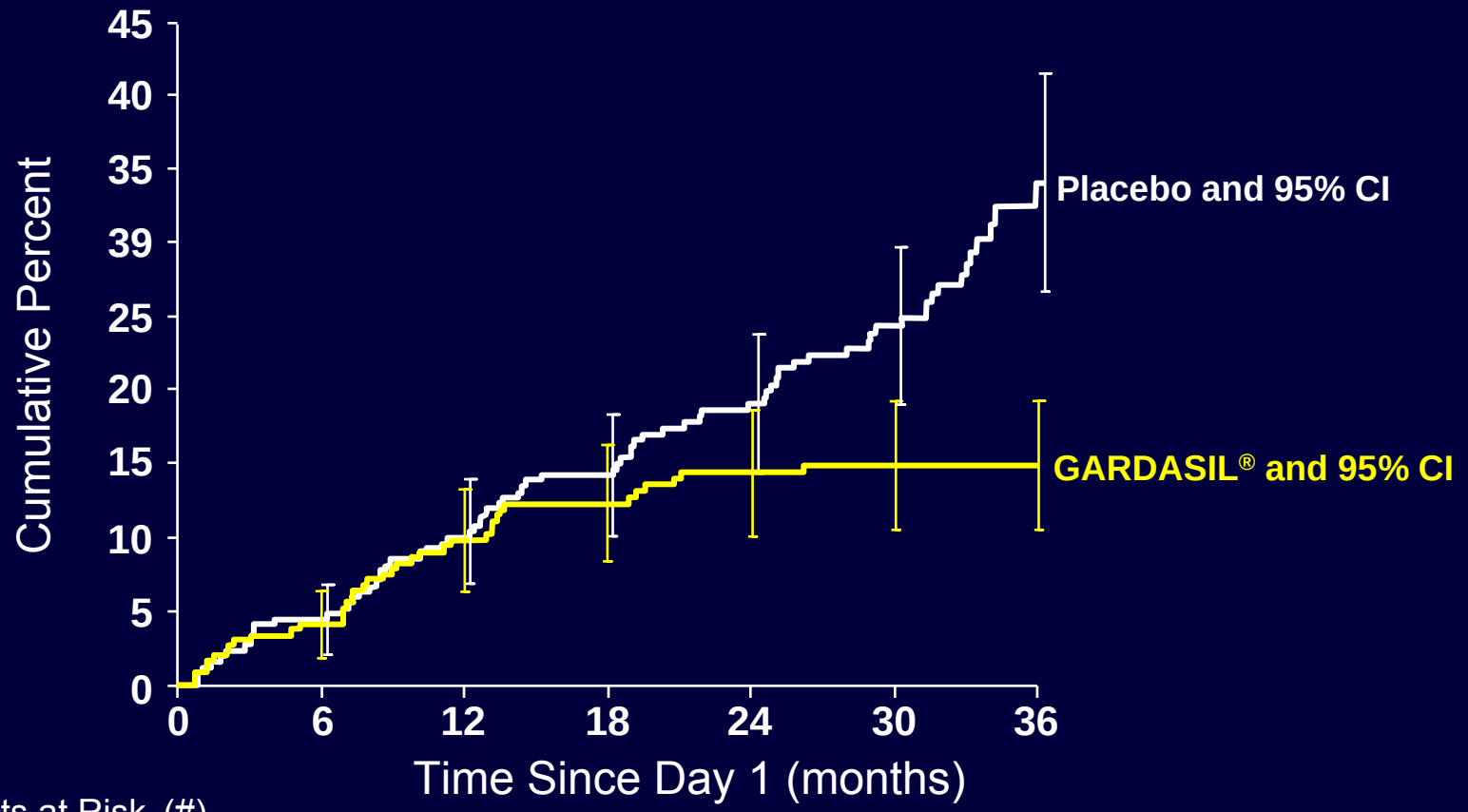
FAS Efficacy Population

Endpoint	GARDASIL® Cases (n=275)	Placebo Cases (n=276)	% Efficacy	95% CI
AIN or anal cancer	38	77	50	26, 67
AIN 1	31	62	50	21, 68
AIN 2/3	18	39	54	18, 75
Anal cancer	0	0	NA	NA

n = number of subjects in FAS population with at least one follow-up visit after Day 1; AIN includes AIN 1, 2, 3.
HPV = human papillomavirus; FAS = full analysis set; CI = confidence interval.

Time to Detection of HPV 6, 11, 16, 18-Related AIN

Full Analysis Set



Subjects at Risk (#)							
GARDASIL	275	264	225	208	191	148	45
Placebo	276	263	236	218	192	146	38

HPV = human papillomavirus; AIN = anal intraepithelial neoplasia; CI = confidence interval.

GARDASIL® is Efficacious Against Anal Infection and Disease

- HPV 6/11/16/18-related AIN
- AIN 2/3 related to:
  - HPV 6/11/16/18
  - HPV 16/18
- Persistent anal HPV 6, 11, 16, 18 infection

HPV = human papillomavirus; AIN = anal intraepithelial neoplasia.

Agenda

- Joel Palefsky, MD
  - Anal HPV infection, AIN and anal cancer
- Patrick Brill-Edwards, MD
  - Current status of GARDASIL®
  - Proposed indication
- Elizabeth Garner, MD, MPH
  - The role of HPV in anal cancer in men and women
  - The burden of anal cancer in men and women
  - High-grade anal intraepithelial neoplasia (AIN 2/3): the precursor of anal cancer
  - AIN study design and results
  - Postlicensure surveillance and longer term studies
  - Rationale for an anal cancer indication in males and females

Post-licensure Longer-Term Assessment of Safety and Effectiveness

- Merck has implemented a comprehensive risk assessment plan for GARDASIL®
- Merck is conducting ongoing longer-term safety and effectiveness studies
  - Extensions of:
    - Adolescent study in males and females
    - Efficacy studies in men and women
  - Postlicensure safety studies
- Safety surveillance through monitoring of spontaneous safety reports

Long-Term Follow-up of Male Efficacy Study Subjects

- Long-term extension comprises regular follow-up of eligible subjects for up to 10 years from enrollment into base study
- All subjects who agree to participate will be evaluated for safety, immunogenicity, and development of EGLs
- MSM subjects will be evaluated for anal disease with annual anal cytology and biennial HRA

EGL = external genital lesions; MSM = men who have sex with men; HRA = high-resolution anoscopy.

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The Totality of Evidence Supports an Anal Cancer Indication in Males and Females

- MSM were studied due to high rates of anal HPV infection and disease
  - Anal HPV infection and disease are not limited to MSM
- The same predominant HPV types cause anal cancer in heterosexual men and women as in MSM
- There are no gender or population-specific characteristics of HPV-related anal cancers → anal cancer is the same disease in MSM, heterosexual men and women
- GARDASIL® is efficacious in all studied populations → AIN efficacy in MSM should reflect efficacy in heterosexual men and women

MSM = men who have sex with men; HPV = human papillomavirus; AIN = anal intraepithelial neoplasia.

Prevention of Anal Cancer Is an Unmet Need in Men and Women

- Anal HPV infection is common in both genders and difficult to prevent
- Many risk factors for anal cancer are common in the general population
- Anal cancer incidence and mortality are increasing in men and women
- Screening of the general population is not practical

An alternative method to prevent anal cancer is needed

HPV = human papillomavirus.

Prevention of Anal Cancer Is an Unmet Need that Can be Addressed by GARDASIL®

- HPV types 16 and 18 cause most anal cancers in men and women
- Preventing AIN 2/3 through primary prevention of anal HPV infection will prevent HPV-related anal cancer
- GARDASIL is efficacious against anal HPV infection, AIN, and AIN 2/3
- Vaccination of individuals prior to sexual debut will provide the greatest public health benefit
- The AIN efficacy data extend the benefits of GARDASIL to include prevention of anal cancer in men and women

HPV = human papillomavirus; AIN = anal intraepithelial neoplasia.